The Archives of Internal Medicine

Vol. XIII MARCH, 1914 No. 3

A PULMONARY ATTACK SIMULATING PRIMARY LOBAR PNEUMONIA, CAUSED BY PULMONARY EMBOLISM AND INFARCTION FROM A LATENT VENOUS THROMBOSIS *

LEWIS A. CONNER, M.D.
NEW YORK

In the course of the past two years I have encountered several cases of acute pulmonary disease supervening in apparently healthy persons, which have been admitted to the hospital with the diagnosis of acute lobar pneumonia, but in which the subsequent course of the disease has made it evident that the true condition was that of pulmonary embolism and infarction, resulting from a venous thrombosis which, at the time of the onset of the illness, was latent. These cases would almost certainly have passed for instances of atypical pneumonia with a complicating venous thrombosis, had it not been for the fact that at this time I was interested in observing the clinical manifestations of thrombophlebitis as it occurs in the course of typhoid fever, and had been much impressed by the frequency with which pulmonary embolism occurred before any local signs of thrombosis could be detected. The results of these observations are recorded in two recent publications.[1, 2]

Before proceeding to an account of the cases which form the basis of this paper, it is desirable, for the better understanding of the subject, to call attention to certain facts which lack the widespread recognition they deserve. Most of these facts have been discussed at some length in the papers just referred to.

1. In the common forms of venous thrombosis, such, for example, as is seen as a complication of typhoid fever, and such as so often

* Submitted for publication Nov. 7, 1913.

* From the Department of Medicine of Cornell Medical College and the Medical Service of the New York Hospital.

* Presented at the Section on Medicine of the Seventeenth International Congress of Medicine, London, 1913.

1. Conner: Pulmonary Symptoms as Premonitory Signs of Venous Thrombosis, Med. Rec., New York, April 29, 1911.

2. Conner: A Contribution to the Symptomatology of Thrombophlebitus in Typhoid, The Archives Int. Med., 1912, x, 534.

supervenes after childbirth and after certain surgical operations, there is regularly a period of days or even weeks during which the course of the thrombosis is either altogether latent or is indicated only by slight and equivocal symptoms; and the classical signs of phlegmasia alba dolens appear only late in the process, or may indeed be lacking altogether. The truth of these assertions is attested by various French writers on the subject (Vaquez,[3] Widal and Besancon[4]), and was demonstrated in many of my own cases. Moreover, the recent histologic studies of Aschoff[5] have shown that the formation of the primary or white thrombus is the result of the gradual deposition of blood platelets on the walls of the still patent vein, layer on layer, in a manner somewhat comparable to the formation of a bar by the deposit of silt in a flowing stream. There is reason to believe that the characteristic local signs of thrombophlebitis appear only after the occlusion of the vein has become complete, and after more or less periphlebitic inflammation has been added.

2. Pulmonary embolism and infarction is a much more frequent complication of venous thrombosis than is commonly supposed. It occurs in two quite distinct forms, which differ much in their time of appearance, their clinical course, and their prognosis. There is first the massive and usually fatal embolus caused by the separation and mobilization of a large fragment of a thrombus, occupying and occluding some such large vein as the femoral or iliac. The emboli occur late in the process of thrombosis and are fortunately rare; but because of their suddenness and the gravity of their symptoms, they are the ones to which attention has been chiefly directed. The second form of pulmonary embolus is of much more frequent occurrence. It appears early in the process of thrombosis, often, indeed, days or even weeks before the local signs of thrombophlebitis are recognizable, so that frequently it is the very first manifestation of that condition. Its symptoms are usually mild and are often interpreted as those of an ordinary pleurisy or pneumonia. These small, early emboli almost certainly arise from the separation of tiny particles from the primary, mural thrombus while the blood is still flowing in the affected vein. This thrombus, as has been said, is formed by the gradual deposit of agglutinated blood platelets, and it is easy to see how such freshly deposited clumps of platelets should be separated from the thrombus and carried away in the blood-stream to be lodged finally in the lung capillaries.

3. Vaquez: De la phlébite, Clin. méd. de la charité, 1894.

4. Widal and Bezancon: Maladies des Veines, Nouveau traité de méd. et de thérap., vol. xxv.

5. Aschoff, et al.: Beiträge zur Thrombosefrage, Leipzig, 1912.

3. Venous thrombosis occurs not so very rarely in individuals who are apparently in good health, or who at least are not obviously sick. The literature contains many instances of such thrombosis in girls with simple chlorosis, in men with gout, in cases of varicose veins of the legs, and even in persons who seem to be quite well. In some of these latter cases syphilis seems to be the underlying cause of the trouble.

If now the above mentioned facts are borne in mind; namely, the period of latency in venous thrombosis; the frequency with which pulmonary infarction occurs before the appearance of the local evidence of thrombophlebitis, and finally the occasional development of venous thrombosis in persons who are apparently in good health; the evidence furnished by the four cases now to be presented, will, it is believed, be found to be convincing that the cases were actually instances of pulmonary embolism and infarction, and were not examples of primary pneumonia, as they at first appeared to be. Unfortunately the evidence of this fact is purely clinical, as the cases all recovered; but this is true also for most of the cases of early pulmonary infarction seen with the venous thrombosis which complicates typhoid fever. Nevertheless, in these latter cases the clinical evidence is overwhelming, as a reference to the articles already referred to will show. The present cases are analogous in every respect to those already reported as complicating typhoid fever.[2]

CASE REPORTS

CASE 1.—Male, 27 years old, a stationary fireman; admitted to New York Hospital March 15, 1912. Hospital No. 181686.

Family history unimportant. Scarlet fever in childhood. Gonorrhea one year ago. No other illnesses. Luetic infection denied. Drinks beer in moderation. Present illness began suddenly two days ago, while in usual good health, with sharp pain in left chest, made worse by coughing or deep breathing. About the same time he began to cough and to raise bloody sputum. Does not know whether or not he has had fever. No other symptoms. No chill. The pain in the chest, cough, and bloody sputum have continued.

Admission temperature 102 F., respirations 42, pulse 120.

Physical Examination.—Man of large frame, muscular, and well nourished. Skin and mucous membranes of good color. Pupils equal and normal. Teeth good; marked pyorrhea alveolaris. Tongue coated and moist. Throat normal. Chest well formed. Expansion somewhat restricted on left side. Respirations rapid. Right lung shows normal physical signs both front and back. Left chest somewhat hyperresonant in front. Posteriorly over the greater part of the left lower lobe there is dulness, with diminished breath and voice sounds and a few fine râles.

Heart apex beat not seen or felt. Relative dulness extends 4.3 cm. to right of midline in third space and 8 cm. to left in fifth space. Heartsounds clear. Slight accentuation of second sound over aortic area. No murmurs. Pulse equal, regular. Tension normal. Slight thickening of the palpable arteries. Liver dulness extends, in nipple line, from sixth rib to 1 cm. below costal margin. Liver edge not felt. Abdomen soft; no tenderness or muscular rigidity. Kidneys and spleen not palpable. Abdominal and cremasteric reflexes normal. Genitalia nor-

mal. Knee jerks equal and normal. No Babinski reflex. Superficial lymph-nodes not enlarged.

March 16. Pain in chest severe during night, requiring morphin. More comfortable to-day. Sputum abundant and frankly bloody. Leukocytes 10,900; polymorphonuclears 81 per cent., mononuclears 19 per cent.

March 17. Slept better. Dulness over left lower lobe posteriorly, with bronchial voice, and breath sounds heard about and below lower angle of scapula. Elsewhere feeble breath sounds. A few crepitant râles.

March 18. Still coughing and raising bloody sputum. To-day there is dulness and bronchial breathing over both lower lobes posteriorly. Much pain on coughing.

March 19. Coughing much through night. On right side posteriorly dulness from fifth space to lower angle of scapula, and flatness from this point to base of lung. About the lower angle of scapula the voice and breathing are bronchial. Below this the voice is nasal and the breath sounds faint and indistinct. On the left side posteriorly the signs are very similar to those on the right, except

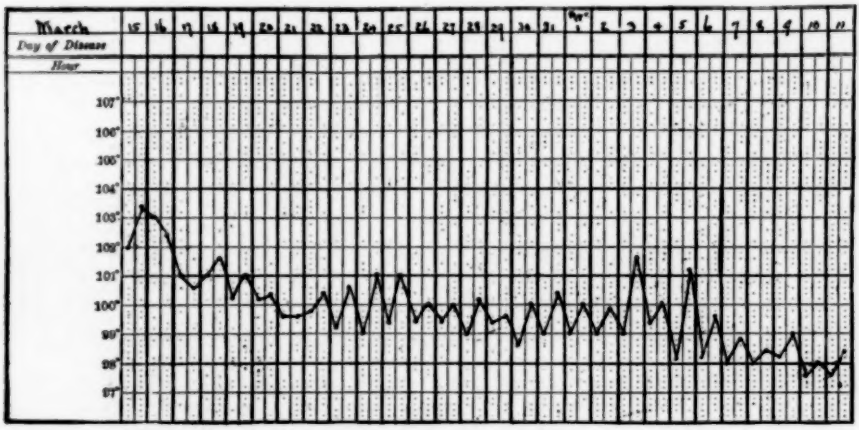

Fig. 1.—Temperature chart Case 1.

that the area of flatness is rather greater, and that a few râles are to be heard. Leukocytes 6,500, polymorphonuclears 66 per cent., mononuclears 34 per cent. Widal test negative.

March 20. Wakeful during the night with severe sharp pain in right leg. The pain and tenderness to-day extends from the ankle up the calf almost to the knee, and there is distinct swelling of the limb. Circumference of right calf, 13 cm. below tip of patella, 34.5 cm.; of left, 32.5 cm.

March 22. Sputum still bloody. Over both chests posteriorly from one inch below angle of scapula to base there is flatness, with faint bronchial breathing, nasal voice, and greatly diminished fremitus.

March 24. Pain and tenderness in right calf have subsided. Signs in chest unchanged.

March 25. A needle inserted in lower part of right chest behind revealed no fluid.

March 26. To-day there is pain and tenderness over the anterior and inner aspects of right thigh along the course of the femoral vein.

March 29. Chest signs unchanged. Sputum still blood-tinged. Still pain and tenderness over right femoral vein. Leg edematous.

April 1. Over left chest behind there is still a small area of dulness and bronchial breathing below angle of scapula. On the right side, from seventh rib to base, the breath sounds are absent and the voice greatly diminished. Sat up in chair.

April 3. Slight dulness at base of right chest. Elsewhere the signs are almost normal. Sputum still blood-tinged.

April 9. Signs in both chests posteriorly have disappeared. Leg still edematous.

April 13. Patient discharged from hospital well, except for some edematous swelling of right leg.

The urine, on admission, was scanty and contained 1.2 gm. of albumen to the litre and many hyalin and granular casts. Later it became quite normal except for the presence of a faint trace of albumin.

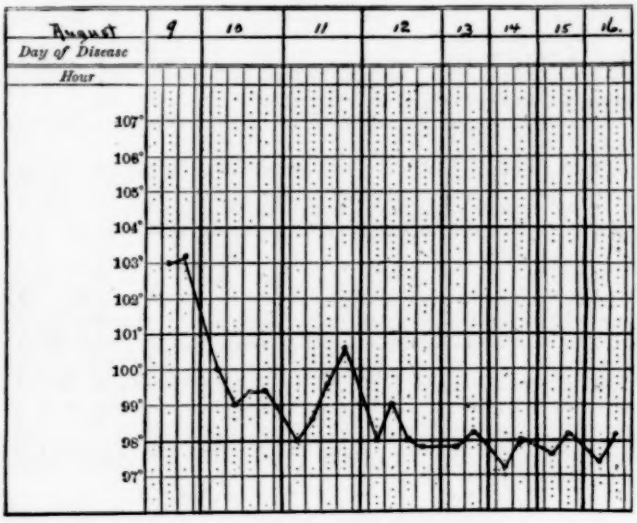

Fig. 2.—Temperature chart Case 2.

CASE 2.—A man, 51 years old, an artist, was brought to the hospital by the ambulance on the afternoon of Aug. 9, 1912, with the diagnosis of lobar pneumonia. Admission temperature 103, respirations 24, pulse 96.

His father had died of cirrhosis of the liver, his mother of pulmonary tuberculosis. He himself had had two attacks of "muscular rheumatism" many years before. In 1897 he had contracted lues with secondary symptoms and had been treated for six months with mercurial inunctions and injections. In 1907 he had ulcers on his extremities and trunk which lasted almost a year. Several attacks of gonorrhea. Uses alcohol to excess, with occasional periods of abstinence.

Present Illness.—On the evening of August 7 patient had sudden cramp-like pain in the suprasternal notch along the left side of the neck to the angle of the jaw. This lasted for several hours and was somewhat relieved by hot applications. At 4 o'clock on the morning of August 9 he was awakened by very severe pain referred to the costal margin on the left side. The pain was made worse by every attempt to take a deep breath. At the same time he began to cough and to raise sputum which, at first, was streaked with blood but soon became thoroughly

bloody. During the day his pain and dyspnea became so severe that an ambulance was called.

Physical Examination.—Body well developed and well nourished. Skin and mucous membranes somewhat cyanotic. Breathing labored, shallow, and painful. Pupils and ocular movements normal. Teeth fair. Tongue moist and slightly coated. Pharynx and tonsils normal. Neck shows nothing abnormal. Over both chests in front and the right chest behind, the physical signs are normal. On the left side, at the level of the lower angle of the scapula in the posterior axillary line, is a small area over which the breath sounds are bronchial. No distinct impairment of resonance or increased voice sounds. Over this area and over the entire left base, extending well into the axilla, are heard many subcrepitant râles.

The heart apex beat cannot be seen nor felt. Relative cardiac dulness extends from the right border of the sternum to 10 cm. to the left of the midline in the fifth space. Heart action regular, moderately rapid. Sounds clear and of good quality. No murmurs. Aortic second sound somewhat accentuated. Pulse of good force and normal tension. No evidence of arteriosclerosis. Liver dulness normal. Liver edge not palpable. Spleen and kidneys not palpable, and abdomen otherwise negative. Extremities: No edema. Tibiae normal. Reflexes normal. Superficial lymph-nodes not enlarged. The sputum contains a large amount of quite bright blood evenly distributed. No clots.

Leukocytes 22,500, polymorphonuclears 90 per cent., mononuclears 10 per cent. Urine normal.

August 10. Patient slept little because of the pain and cough. Somewhat more comfortable to-day. Temperature much lower. Sputum still bloody.

August 11. Sputum contains less blood. No pain in chest.

August 12. To-day no bronchial breathing to be heard over left lower lobe but the râles persist.

August 13. No blood in sputum. Pulmonary signs unchanged. Careful questioning elicits the fact that several days before the onset of the present illness he had some pain in the calf of his right leg, which soon disappeared and has not returned. In the left calf can now be felt a small indurated cord, which is not tender to pressure.

August 16. Steady improvement. Signs in left lung have disappeared. Up in chair. Several examinations of the sputum for tubercle bacilli were negative.

August 19. Discharged cured.

CASE 3.—Male, 51 years old, elevator-man. Admitted to hospital January 9, 1913. No. 186327.

Family history unimportant. Since boyhood patient's general health has been good. Severe attack of tonsillitis at 24 years of age. Troublesome sciatica in right thigh from time to time for many years. Gonorrhea at 20 years. No sequelae. Denies lues. Steady drinker of beer and whisky up to two years ago. Since then has drunk very moderately.

Six weeks before admission he first felt a dull pain in the right calf, associated with slight swelling. No swelling or edema of the rest of the leg. Pain never severe enough to keep patient from work.

Present illness began on the evening of January 5 with chilliness and fever. On the following day he was seized with sudden, severe pain referred to the right upper quadrant of the abdomen and with headache and nausea. The pain soon shifted to the left upper quadrant, and has since been felt at various places in the upper part of the abdomen. In addition to the pain there has been fever, cough with scanty sputum, flatulence and abdominal distention, and quite marked dyspnea. On January 9 the patient was admitted to the surgical side of the hospital, in the service of Dr. Hitzrot.

Admission temperature 101, respirations 36, pulse 100.

At that time the marked abdominal distention, the pain referred to the epigastrium and left hypochondrium, together with some tenderness and slight muscular rigidity, suggested that the trouble was some inflammatory condition in the

upper part of the abdomen. Examination of the chest revealed nothing except the presence of a few fine râles at the base of both lungs posteriorly.

The leukocytes numbered 13,800, polymorphonuclears 84 per cent., lymphocytes 13 per cent., large mononuclears 2 per cent., eosinophils 1 per cent.

January 10. Coughed a good deal through the night. Pain in lower part of left chest, especially on coughing.

For the next two days the symptoms persisted almost unchanged. The pain was located sometimes at the base of the left axilla, sometimes in the epigastrium, and sometimes in the right hypochondrium. The dyspnea continued and the cough grew more troublesome. The sputum was scanty and free from blood. On January 12 some impairment of resonance and a small area of faint bronchial breathing could be made out at the left base posteriorly, and subcrepitant râles were numerous over the lower part of both lungs. It became evident that the condition was not a surgical one, and the patient, on January 13, was transferred to the medical service, with the diagnosis of pneumonia.

Physical Examination.—Stout, well-developed man. Good color. Tongue moist and heavily coated; teeth poor; pyorrhea alveolaris. Chest broad and deep.

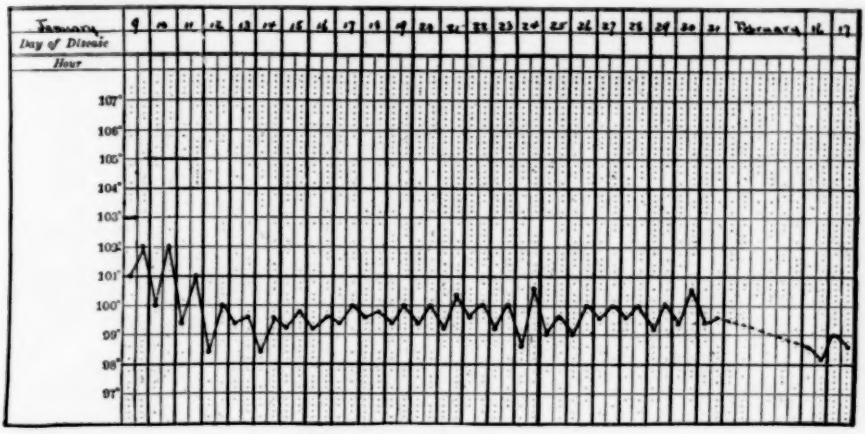

Fig. 3.—Temperature chart Case 3.

Respirations rapid, labored and painful. Lungs: Signs normal anteriorly. In left axilla is heard a coarse, leathery, friction sound. Posteriorly over the lower part of the left lower lobe the percussion note is somewhat impaired and over a small area there is distinct bronchial breathing, somewhat obscured by subcrepitant and sibilant râles, the latter heard chiefly during the much prolonged expiration. Voice sounds increased, but not frankly bronchial. Over the right base posteriorly similar râles are heard. No change in percussion, breathing, or voice sounds.

Heart much enlarged. Relative cardiac dulness extends from 5 cm. to right of midline in fourth space to about 13 cm. to left of midline in fifth space. Impulse diffuse and heaving. Heart-sounds clear. Second sound accentuated at apex and over aortic area. No murmurs. Pulse regular, somewhat rapid and strong. Systolic blood-pressure 180 mm. Arteries slightly thickened. Liver dulness extends from fourth intercostal space to costal margin. Neither liver nor spleen palpable. Abdomen full, tympanitic, and slightly tender in right upper quadrant. No muscle spasm. Genitalia normal. Extremities show no scars nor edema. Tendon reflexes normal.

January 14. The signs of consolidation at right base have disappeared. A few râles still to be heard at both bases. The urine at each examination shows a heavy precipitate of albumen (about 4 gm. to the litre), high specific gravity and many hyalin and granular casts. There is marked retention of chlorids. The phenolsulphonephthalein test shows an excretion of only 16 to 20 per cent. in two hours, and the lactose test shows the excretion of only a trace of lactose in fourteen hours.

January 21. Patient has been sitting up for two days. To-day there is pain and tenderness in right calf and over inner side of right thigh. There is also tenderness in the heel and between the first and second metatarsal bones. No edema of foot or leg. The appearance of these unmistakable signs of venous thrombosis gave the first clue to the true nature of the pulmonary lesions.

On the morning of January 26, the patient was awakened with pain in the left leg, with later tenderness in the calf and sole. During the next three days there appeared the signs of an extensive thrombophlebitis, involving the left femoral and popliteal veins, and those of the calf and foot. The signs in both

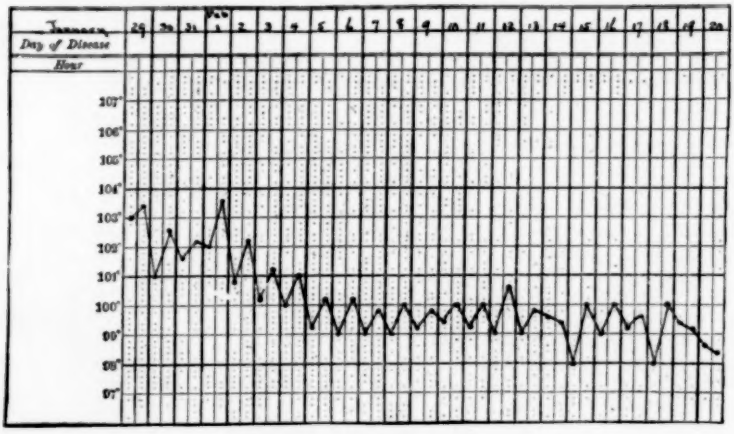

Fig. 4.—Temperature chart Case 4.

legs gradually subsided in the course of the next two weeks, but some edema of both legs persisted up to the time of his discharge from the hospital, on February 22.

CASE 4.—Female, unmarried, 63 years old. No. 186702. Admitted to the hospital on Jan. 29, 1913, with the diagnosis of lobar pneumonia.

Her present illness had begun suddenly on January 26, with severe pain in the right chest, high fever, cough, and headache. The pain was much increased by deep breathing or by coughing. The symptoms have continued, and with the cough she has occasionally spat up small amounts of clotted, bloody sputum.

Up to the time of her present illness, her general health had been remarkably good. She has had occasional attacks of cramps and diarrhea and, two months before, an attack of influenza, but otherwise had always been well.

Physical Examination.—A poorly-nourished, slender woman, with flushed face and slight cyanosis of lips. Respirations rapid and painful. The pulmonary signs over both chests in front are normal. In the right axilla a coarse friction-rub is felt and heard. Posteriorly over the lower half of the right lower lobe there is dulness on percussion, almost complete suppression of the breath sounds, and many fine crackling râles. The vocal resonance shows no distinct change.

Over the rest of the right lung and over the whole of the left lung posteriorly the signs are normal. Heart: Apex beat indistinctly felt. Relative cardiac dulness extends from the right border of the sternum to 8.5 cm. to left of the midline in the fifth space. Heart-sounds are clear. Slight accentuation of aortic second sound. Pulse small, rapid, regular, and of fairly good force. Arteries somewhat thickened. Abdomen negative. No edema of the extremities.

Admission temperature 103 F., respirations 30, pulse 108. Urine normal.

During the next two days the physical signs and the general condition of the patient remained practically unchanged. The sputum was scanty and showed small clots of dark blood. The dulness, indistinct breath sounds, and crepitant râles made it obvious that there was a localized lesion in the right lower lobe, although frank bronchial breathing was never heard.

Leukocytes 14,400, polymorphonuclears 80 per cent., lymphocytes 17 per cent., large mononuclears 3 per cent.

January 31. Condition somewhat improved and pain less. Sputum no longer bloody.

February 2. After two days and nights of comparative comfort, there is again severe pain in right side.

February 5. Signs in right lower lobe are clearing up. Still some crepitant râles to be heard. General condition much improved.

February 9. Some pain in right side during the preceding night.

February 11. Sitting up in chair.

February 16. To-day patient had sudden severe pain in left axilla where a few fine râles can be heard. The appearance of sudden pain and of râles in the other side of the chest, together with the frankly bloody character of the sputum at the onset suggested that the condition might be one of pulmonary infarction, rather than of primary pneumonia. A careful examination of the legs revealed a tender cord, about the diameter of a small lead pencil, extending along the inner side of the right thigh from a point just above the knee to the saphenous opening, and obviously representing the thrombosed internal saphenous vein. There was no periphlebitis. On being questioned the patient stated that she had noticed these "clotted veins" in the right thigh for two or three weeks, but had not spoken of them as they gave her little trouble.

On the following day the pain in the left chest was less. The râles could still be heard, but there were no signs of consolidation and but little cough.

By February 20, all the pulmonary signs had disappeared, the tenderness had gone from the thrombosed vein and the patient was able to be moved to the convalescent home at White Plains.

DISCUSSION

In Case 1 the onset was exactly like that of a primary pneumonia, except for the absence of a rigor, and no doubt was entertained at first as to the correctness of the diagnosis. But the frankly bloody character of the sputum, which continued day after day, soon raised a suspicion of the true nature of the condition, and we were able to predict with some assurance the ultimate appearance of the venous thrombosis, which gave its first local signs seven days after the onset of the pulmonary symptoms. In this instance the bloody sputum lasted for twenty-one days. Concerning the physical signs, it is to be noted that the signs of consolidation appeared first in the left lower lobe, and a few days later in the right lower lobe, and that gradually these signs changed so as to give the impression that there was present more or less fluid in both pleural cavities, although the aspirating needle failed to show

any. In the above mentioned study[2] of a large number of cases of pulmonary embolism and infarction complicating typhoid fever the cases, with respect to their physical signs, could be divided into three well marked groups:

1. Those in which friction-rubs or crepitant râles, over a small area, were the only signs. These signs often lasted only two or three days.

2. Cases in which the signs were those of a small, circumscribed pneumonia. The area of consolidation did not extend, and in each instance the signs of consolidation disappeared within three or four days. These signs were almost always in the lower lobes.

3. Cases with signs of extensive plastic pleurisy or of pleural effusion. This type included more than half of all the cases. In some of these the physical signs at first were those of consolidation. It seemed quite characteristic of the third group of cases that, although the signs seemed to indicate the presence of liquid, exploratory puncture usually failed to reveal it. In the case under discussion the physical signs corresponded accurately with those in the third and largest group just quoted.

In Case 2, a luetic man, the physical signs were those of a small area of consolidation near the lower angle of the left scapula, which disappeared within two or three days. In this case also the sputum was composed chiefly of blood and bore no resemblance whatever to the rusty, tenacious sputum of pneumonia. On questioning the patient, the fact was elicited that several days before the appearance of pulmonary symptoms he had had, for a day or two, some pain in the calf of his right leg. When first seen by me, toward the end of his illness, a distinct indurated cord could be made out in the left calf, which did not correspond to any of the normal structures there, and which seemed to me clearly to represent a thrombosed and thickened vein. A very interesting feature of this case was the appearance of sudden and severe pain in the left side of the neck and in the suprasternal notch, which came on some thirty-six hours before the advent of pulmonary symptoms. The peculiar location of this pain, Capps[6] has shown to be characteristic of irritation of the central portion of the diaphragmatic pleura, and in this instance the pain suggests that there had been a small infarct somewhere on the central portion of the lower surface of the lung before the occurrence of the larger infarct, which gave the more characteristic symptoms and signs.

Case 3 was that of a man with fairly marked chronic nephritis, which, however, did not prevent him from carrying on his daily work

6. Capps: An Experimental Study of the Pain Sense in the Pleural Membranes, THE ARCHIVES INT. MED., 1911, viii, 717.

—an occupation that required him to be constantly on his feet. In this instance the diaphragmatic location of the infarct is seen by the fact that the symptoms (pain, tenderness and muscular rigidity) were at first abdominal rather than thoracic. In this case (the only one among the four) the sputum was very scanty and was at no time bloody. The signs of consolidation lasted only about two days. The clue to the true diagnosis came only when signs of phlebitis appeared some days after the pulmonary signs. Then was elicited the fact that, for several weeks before his illness, he had had dull pain and soreness in the right calf, with some local swelling.

In Case 4, the interesting features were the character of the sputum, and the fact that two weeks after the subsidence of the first pulmonary attack there were indications of the occurrence of a small embolus in the other lung.

To recapitulate, then, we have in three of the four cases sputum which consisted chiefly of liquid or clotted blood, and in no case sputum which bore any resemblance to the characteristic sputum of pneumonia; in every case the physical signs differed in some respect from those usual in pneumonia—in two cases by the short duration of the signs of consolidation, in one by the absence of frank signs of consolidation, and in one by the anomalous and protracted pleural signs; in all the cases there were indications that the pulmonary lesions were multiple; in none of the cases was there an introductory rigor; in three of the four cases the temperature chart bore little resemblance to the usual chart of pneumonia, and, finally, in three of the four cases there were points in the history to indicate that venous thrombosis existed before the onset of the pulmonary symptoms.

No one of these facts alone would be entitled to much weight in the attempt to differentiate these cases from those of primary pneumonia, but taken together they form a mass of evidence sufficient, I think, to warrant the conclusion that all of these cases were instances of pulmonary embolism and infarction.

How frequent such instances of pulmonary infarction in apparently healthy persons may be it is impossible to say, but the fact that four such cases were observed in a single medical service during the period of one year suggests that they are far from rare, and that they are worthy of consideration and study.[7] That it may be quite impossible at times to say positively whether the venous thrombosis, which declares itself after the appearance of the pulmonary trouble, is the cause or merely the result of this is freely admitted, but in most cases a careful study of the symptoms and a patient inquiry into the history of the

7. Since this was written two additional cases of the same sort have been treated in the wards of the New York Hospital.

case will, I believe, provide one with sufficient data to clear up the uncertainty. It is interesting to note that, forty years ago, Gerhardt,[8] in his classical study of pulmonary infarction, emphasized the fact, that "often the appearance of the embolic lung infarct furnishes the first firm support for the diagnosis of venous thrombosis."

8. Gerhardt: Der hämorrhagische Infarct, Volkmann's Saml. klin. Vortr., 1875, No. 91.

THE COMPARATIVE VALUE OF CARDIAC REMEDIES*

THEODORE C. JANEWAY, M.D.
NEW YORK

I. Introduction.
II. Effects of Digitalis on the Normal Circulation.
III. Drugs in Cardiac Insufficiency with Auricular Fibrillation.
A. Acute, in mitral disease.
B. Chronic, in mitral disease.
(*a*) Strophanthin.
(*b*) Digitalis.
C. In other rapid, fibrillating hearts.
(*a*) In aortic disease.
(*b*) In chronic nephritis.
(*c*) In myocardial disease.
(*d*) In paroxysmal tachycardia.
(*e*) In cases with paroxysmal dyspnea.
(*f*) In cases with active endocarditis.
IV. Drugs in Cardiac Insufficiency with Normal Rhythm.
A. In hypertensive cases.
(*a*) Digitalis.
(*b*) Caffein and allies.
B. In primary myocardial insufficiency.
C. In mitral disease.
D. In aortic disease.
E. In failure of the right ventricle.
F. In exophthalmic goiter.
V. Drugs in Other Disturbances of Rhythm.
A. In paroxysmal tachycardia.
B. In heart block.
C. In extrasytolic irregularity.
VI. Drugs in Angina Pectoris.
VII. The Treatment of Recent Endocarditis and Initial Cardiac Insufficiency.
VIII. Conclusions.
Bibliography.

I. INTRODUCTION

At an international congress of medicine held in the city where William Harvey announced his discovery of the circulation of the blood, in the land where Withering first made the therapeutic virtues of the foxglove the subject of scientific inquiry, it is fitting that a section presided over by the eminent therapeutist to whom we owe the nitrites should discuss the comparative value of cardiac remedies. Twelve years ago, in a similar discussion before the nineteenth congress of internal

* Report presented before the Section on Therapeutics (Pharmacology), Physio-Therapy and Balneology of the XVII International Congress of Medicine, London, August, 1913.

medicine at Berlin, Professor Sahli said: *"Allein die Handhabung der Digitalis ist eine grosse Kunst, und wie in jeder Kunst, so erreicht man auch hier kaum den Gipfel der Vollendung."* No more complete demonstration of this could be afforded than the added knowledge of this very drug which the clinical studies of the twelve intervening years have contributed. The literature of the clinical investigations of cardiac remedies is now so vast that an attempt to give proper credit to the workers in the field is out of the question. I shall therefore ask pardon in advance for my omissions in this respect.

The limitation of the field of inquiry is difficult. Even the digitalis bodies, the cardiac remedies *par excellence*, have important vascular and nervous actions as well. As far back as 1866, Lauder Brunton pointed out their effect on the arterioles; the subject was subsequently studied exhaustively by Gottlieb and Magnus. This action is quite selective, so that small doses, both of digitalis derivatives and of strophanthin, may dilate the renal, while constricting the intestinal vessels, as Jonescu and Loewi, Kasztan and Fahrenkamp have shown. While Heubner denies that this occurs with therapeutic doses, and Gottlieb himself does not consider it more than highly probable, the studies of Schlayer and Hedinger on the over-irritability of the arteries in experimental nephritis — and in particular the subsequent work of Hedinger — make the strongest presumption in favor of regarding these truly cardiac drugs as at times diuretic, by local vasodilatation in the kidney. This being so, it seems wiser not to exclude from the category of cardiac remedies drugs such as caffein and camphor, whose direct cardiac action is denied by some pharmacologists — Cushny, for instance — and which act mainly on the arteries and vasomotor center. The estimation of the share of heart and vessels in a circulatory disorder is not always possible. I shall therefore consider cardiac remedies rather broadly, as circulatory remedies. I shall give my experience with the various drugs in those disturbances of the circulation in which the heart plays any part, from the standpoint of their efficiency in combating definite perversions of function. From this standpoint we may arrive at greater precision in formulating the indications for and against the several remedies which, with Edens, I believe is the chief difficulty attending their use.

Since the time of Withering, every intelligent physician has recognized the clinical picture of the insufficient heart, with chronic passive congestion of the viscera and edema, as the strictest indication for the use of digitalis or its allies. It has also been clear that the most brilliant results are obtained in the rapid, irregular heart of mitral disease. Perhaps the most important contribution to cardiac pathology and therapy for the past ten years is the proof by Lewis that the *delirium cordis* of past generations, the *pulsus irregularis perpetuis* of Hering, the nodal

rhythm of Mackenzie, are the ventricular manifestations of fibrillation of the auricles. This was made possible by Einthoven, whose string galvanometer has brought the disorders of the heart's rhythm into the range of exact clinical observation; and by the pioneer work of Wenckebach, Hering and Mackenzie in this field. Lewis followed this demonstration by the proof that in man the slowing and steadying of the ventricle under digitalis is due to its action on the junctional tissues, with the production of heart block, just as in von Tabora's experimental studies. Since that time the attention of English and American clinicians and pharmacologists has been focused almost wholly on the effects produced by the digitalis bodies on the cardiac rhythm, because these effects are susceptible of exact demonstration. Other effects entering into the therapeutic action of these drugs have been neglected or ignored. This attitude does not seem so common in Europe. The extreme view was expressed by Cushny in his Harvey lecture for 1911 as follows: "But I think I am safe in stating that we have no definite evidence that digitalis exerts any action apart from the inhibition in these cases of auricular fibrillation, and that the proved fact of inhibition explains all the features observed." At that time Cushny believed digitalis block to be wholly due to vagus inhibition. Recently he has reversed himself (Cushny, Morris and Silberberg). From experiments as to the degree of release after atropin, he concludes that, in normal rhythm, digitalis slowing is usually inhibitory, in fibrillating cases due to direct action on the conducting tissues, direct depression of excitability, or indirect, through improved nutrition of the heart. In a recent discussion on the treatment of non-valvular heart disease he further admits that the effect on the ventricle itself is real, but it is not possible to speak of it with certainty.

Mackenzie expresses himself with somewhat more reserve. His studies of digitalis are a model of thoroughness, and he has been foremost in bringing precision into cardiac therapeutics. He is impressed with the difference in the reaction of individual hearts to the drug, due at least in part to the nature of the lesion; yet his emphasis is entirely on the disturbance of rhythm, and he thinks little of the gross mechanical defect. In a recent text-book article he states his belief in tone increase under digitalis, though he confesses inability to demonstrate any change in the size of the heart.

Such opinions evidence a healthy scepticism, but also the inadequacy of our present clinical methods for measuring the efficiency of the circulation as a whole. The volume output of the heart we cannot even guess at. The peripheral arterial pressures give us a rough indication of the changes in mean aortic pressure, but vasomotor compensation in man is probably so much more perfect than in the lower animals, that this

can in nowise be considered a measure of the heart's work. Improved coronary circulation must be an important factor in enhancing the strength of the heart muscle, whenever the aortic circulation is favorably influenced. Up to the present, our simple clinical observation of the redistribution of the blood from the venous to the arterial side of the circulation with shrinking of the swollen liver, absorption of edema with diuresis, and relief of pulmonary stasis and its attendant dyspnea, must be the evidence for the human ventricle of those systolic and diastolic effects of digitalis which are fundamental actions on the isolated heart, as Professor Gottlieb has shown. They must be subjected to searching criticism and such analysis as is possible, and checked by exact observations of rate, rhythm, blood-pressure, water exchanges, and so forth; but they cannot be supplanted by these. For a proper use of cardiac remedies, I agree with Romberg that the emphasis should be on the dynamic condition of the heart's action. Fraenkel's contributions to our knowledge of digitalis therapy have not lost their value because they preceded the era of the polygraph, nor have Huchard's opinions; but they must be amplified and corrected. I would focus your attention, therefore, on the efficiency of the circulation and our ability to influence it.

II. EFFECTS OF DIGITALIS ON THE NORMAL CIRCULATION

It seems clear from all pharmacological studies, from such experiments with long-continued digitalis administration as Cloetta's, and from Fraenkel and Schwartz's intravenous strophanthin injections in normal men, that the effects of digitalis on the normal circulation are minimal unless the drug is pushed to the point of intoxication. This fact has often been used as an argument by those who do not believe that digitalis given therapeutically increases the efficiency of the ventricular muscle. I believe, however, that we must recognize that the normal, intact circulation is already working with optimal efficiency and that the perfectly definite systolic and diastolic effects of digitalis on the isolated ventricle are not calculated to enhance this. Whether long-continued administration of digitalis can lead to hypertrophy of the heart, as claimed by Hare and Coplin, no subsequent experiments have determined with any certainty (Cloetta, Gelbart, Wynn).

III. DRUGS IN CARDIAC INSUFFICIENCY WITH AURICULAR FIBRILLATION

A. *Acute, in Mitral Disease.*—The more completely a given circulatory disturbance is dependent on a rapid rate which can be controlled by digitalis, the more brilliant is the therapeutic effect of the drug. The best example of this, in my opinion, is not the extreme cardiac insufficiency with marked chronic passive congestion after long-standing

auricular fibrillation in mitral disease, but a group of cases which I regard as important to recognize clinically. They are the cases of well-compensated mitral disease, in which auricular fibrillation with great tachycardia sets in acutely. As a rule, dyspnea is inconspicuous, the symptoms being great exhaustion on exertion, dizziness, and a tendency to syncopal attacks. These are symptoms rather similar to those seen in paroxysmal tachycardia and have some resemblance to Stokes-Adams syndrome. They are presumably due, in the main, to the sudden change in the cerebral circulation. After some days, enlargement and tenderness of the liver appear, and if the condition is unrecognized and therefore untreated, as I have found it to be by the general practitioner, the full-fledged picture of the decompensated mitral heart will then become manifest later. The tachycardia in these patients can be controlled by digitalis within forty-eight hours with complete relief of the symptoms, and under long-continued digitalis medication such patients may maintain a very fair working ability for several years. It is of the highest importance that treatment be instituted before marked dilatation of the right heart and general venous stasis have ensued.

I recognize clearly that the chief factor in determining the brilliant results in these cases is the auricular fibrillation, because, as Mackenzie and Lewis have demonstrated, the His bundle is peculiarly susceptible to digitalis in fibrillating hearts, the seats of old rheumatic mitral disease. On the other hand, it seems to me equally clear that the mitral stenosis makes the rapid, irregular action especially detrimental to the efficiency of the circulation. In fibrillating types of paroxysmal tachycardia, occurring in hearts not the seat of valvular disease, the circulatory disturbance produced is usually much less marked and the therapeutic results are similarly slight. In cases of advanced mitral disease, on the other hand, while the rate may be as easily controlled, secondary changes in lungs, liver and kidneys already exist, and the extent of the valvular effect is so great as to preclude the re-establishment of even fairly efficient circulation after the rate has been brought to normal. I believe, therefore, that the three elements contributing to the result in these cases are:

1. The existence of a disorder of the rhythm, against which digitalis is absolutely effective.

2. The existence of a valve lesion, the detrimental mechanical effects of which on the circulation are peculiarly heightened by auricular fibrillation.

3. The acute character of the onset of fibrillation in a heart which would have remained well compensated for years, had not the disturbance of rhythm occurred, and which, therefore, must be considered as having had a good right ventricular myocardium.

B. *Chronic, in Mitral Disease.*—Next to these acute cases of fibrillation in response to digitalis comes the type picture of gradual cardiac insufficiency, with general venous stasis and edema. Here again, if fibrillation be present, the rapidity and completeness of the functional recovery is in almost direct proportion to the heart rate. In other words, the more these cases conform to the acute type that I have described, the more promptly does the control of the tachycardia by digitalis effect a restitution of function. On the other hand, even in rheumatic mitral disease with fibrillation, if the rate be normal or slow, the effect of digitalis treatment may not be evident until it has been administered for a week or more. In some cases, especially with marked tricuspid regurgitation and liver stasis, it may fail entirely. In other cases the drug acts only after the institution of such accessory measures as the extreme fluid and salt restriction of the Karell diet, which I have found of the utmost value. In some of these patients it is altogether probable that failure is due to defective absorption of the drug given by mouth. Ogawa has shown experimentally how markedly portal stasis interferes with the passage of digitalis from the intestine into the circulation. Meyer discusses this very fully in his recent monograph.

(*a*) *Strophanthin.*—It is in these cases of extreme secondary tricuspid regurgitation with pulsating liver that strophanthin intravenously seems the ideal method of administration. My personal experience with it has not been great. I have perhaps been backward in adopting it because of the excellent results that I can usually obtain by the Karell diet. Digitalis following this usually acts with great promptness, even where it has failed before. However, the admirable results obtained with strophanthin by Fraenkel and Schwartz, Fraenkel, Danielopolu, and Bailey, incline me to resort to it more frequently.

The indications, according to Fraenkel and Schwartz, are: (1) In all severe, threatening cardiac insufficiency, dependent on primary cardiac, not vascular or renal, disease; (2) in those cases of subacute and chronic cardiac insufficiency where the patient is so ill that one desires to relieve him in less than forty-eight hours, the time required for effects by mouth; and (3) where the condition of the stomach or bowel, preceding surgical operation, etc., makes internal administration difficult, or where idiosyncrasy to other preparations exists. I am not prepared to adopt the use of strophanthin in chronic cases, except where the existence of very urgent symptoms makes haste imperative, or where portal stasis makes failure with digitalis likely. I agree with Romberg in this respect. In the urgent cases, free venesection is a most important adjuvant measure. When such patients enter a hospital, it must always be remembered that they may have had previous, protracted ambulatory treatment with digitalis. If strophanthin in full doses is then

administered, the summation of this on a small amount of digitalis already fixed in the heart may produce fatal results. Hatcher and Bailey, the most careful students of strophanthin in America, have made this point clear. That in such cases one must wait, as Romberg insists, from ten to fourteen days after the last dose by mouth was given, does not seem to me imperative if digitalis effects on the general circulation and the heart rhythm are found to be absent. It is clear, however, that a small initial dose should be given, and its effect controlled by graphic record of the rhythm. In general practice, however, great caution is wise. Deaths have occurred after strophanthin which I do not believe can be laid to its use, but Chauffard and Troisier's case was clearly a poisoning, and Agassiz's possibly so.

As to the dose, Hatcher and Bailey, and Bailey, have proved that the crystalline g-strophanthin of Thoms, or ouabain, is most certain, and has twice the strength of the amorphous strophanthin of Boehringer or Merck, which is chiefly used in Europe. The dose should not exceed 0.5 mg. in twenty-four hours, and should not be repeated without careful observation of its effects. Hatcher advocates a cat-unit standard equal to 0.1 mg. of ouabain. The intravenous dose of any strophanthin should not exceed five such cat-units.

(*b*) *Digitalis.*—The choice of a preparation of digitalis is, to my mind, largely a matter of taste, provided the one used is known to be effective. For this reason it has been and is the subject of bitter controversy, into which I shall not enter. It is clear that physiological standardization is in every way desirable, but the recent work of Schmiedeberg and of Holste casts doubt on the absolute value of the frog-unit from year to year. Standardization alone will not ensure a reliable product after the apothecary has had it on his shelves. The method of preservation is all-important, as Focke has demonstrated. Given reliable leaves, my personal preference has always been for the infusion, and Dixon's critical review of the subject confirms my opinion. Gottlieb and Ogawa found the infusion absorbed better from the bowel than the powdered leaf. My experience with it, and my father's before me, have been so favorable that I should require strong evidence to make me change. When away from a known supply of good leaves, however, I have come to advocate digipuratum as a uniform and efficient preparation, even after it has been kept for some time. The question of gastric irritation seems to me of little importance, for I rarely see vomiting, except as a later central effect. In America digalen also has been used extensively, but I have not found it reliable, some samples being inert when sold. It is ordinarily used in too small a dose, through a mistaken idea of its strength. It is too irritant for subcutaneous use. The pure digitoxin used in France, Nativelle's crystallin digitalin, I have had no experience with. At

the present day the choice of a preparation, I believe, should lie between standardized leaves, given in powder, as infusion, or as tincture; or digipuratum by mouth, with the only other form of administration the intravenous injection of one of the strophanthins, preferably ouabain. Hatcher's work leaves no room for doubt that, because of its extreme variability of absorption, strophanthus should never be administered orally. One should adhere to the use of a single satisfactory preparation and know it thoroughly, rather than experiment with many, and should allow others to be guided equally by their experience.

As to dosage, I have not found the large doses used by Mackenzie and Cushny to be necessary. I prefer a moderate dose, equivalent to not over 0.1 gm. (1½ gr.) of the leaves every four hours, which will give definite slowing of the pulse and diuresis in forty-eight hours in rapid fibrillating cases. This dose I continue until the pulse falls to near 60 or becomes bigeminal; failing this, until absorption of edema is complete, or nausea, vomiting, headache or other toxic symptoms ensue. As a rule, I avoid these. A most important evidence of favorable action, which Prof. W. B. James has made of great use in the wards of the Presbyterian Hospital, is the graphic record of a simultaneously recorded heart-rate and radial pulse-rate. In rapid fibrillating hearts, the difference, which we call pulse deficit, is usually great; but with digitalis slowing, the two curves approach each other, and may finally correspond. When any of these evidences of full therapeutic action is obtained, the drug is stopped and not resumed until increasing rate or pulse deficit, or disappearance of coupled beats, show the heart to be escaping from its influence, which usually occurs in from five to ten days. Then one-half or three-quarters of the daily amount given before will control all symptoms.

In all fibrillating cases with a tendency to rapid rate, after the original digitalis course, I believe the indications for continued, so-called chronic digitalis treatment are absolute. To me they are as absolute as for continued thyroid administration in myxedema. The efficiency of such hearts depends largely on the maintenance of a normal rate. A normal rate can be obtained by perpetuating the right degree of digitalis block. Sometimes this is optimal when the coupled beats appear, but the limit of dosage has then been reached, and the wiser course in ambulant patients is to keep just below that point, with the intermission of a few days every two weeks. Each case must be considered individually, as in determining the tolerance of a diabetic for carbohydrate, and then seen from time to time. Serious breakdown may thus be prevented for years, provided the heart can be reasonably safeguarded from excessive demands or a new infection, and the lesion be not progressive.

On one point I wish to state my personal opinion unequivocally. Failure to obtain satisfactory results from digitalis therapy in the class of cases just discussed is evidence of an inefficient preparation, insufficient dosage, or an improper mode of administration. I agree entirely with Krehl that, whenever digitalis fails, a second, and then a third trial should be made with a drug obtained from another source. Furthermore, I should urge the need in some cases for employing the accessory measures to which I have alluded.

C. *In other Rapid, Fibrillating Hearts.* (*a*) *In Aortic Disease.*—While the failure of compensation in hearts the seat of old mitral endocarditis is most commonly associated with a rapid ventricular rate and fibrillation, insufficient hearts with other primary lesions occasionally fall into this category. With aortic disease it is rare, and this is probably one of the reasons why digitalis so frequently fails in aortic hearts, though not the only reason.

(*b*) *In Chronic Nephritis.*—In cardiac insufficiency secondary to hypertensive arterial disease, with or without nephritis, fibrillation is also less common. From my personal records, as I shall show subsequently, the response to treatment in these cases is less dependent on the existence or non-existence of fibrillation. I believe this is in part because such rapid rates as in mitral disease are not observed, but also because moderately rapid, irregular action is less detrimental to the delivery of a reasonable minute volume into the aorta against high pressure, than to maintaining the flow through a narrow, unyielding mitral orifice (B. Lewy). The indications for treatment in the nephritic heart, therefore, I shall consider later.

(*c*) *In Myocardial Disease.*—Some elderly people whose hearts exhibit clinically primary myocardial insufficiency show a type of fibrillating tachycardia quite similar to the mitral hearts previously described, and their response to digitalis is in my experience favorable. Schrenck has also had good results in cases of primary myocardial weakness. On the other hand, I have seen patients of this same type in whom the rapid, irregular action had existed for several years, practically without cardiac symptoms. Where a relative mitral regurgitation occurs, I am persuaded from my experience that the effect of digitalis is peculiarly favorable.

(*d*) *In Paroxysmal Tachycardia.*—So far as my personal experience goes, I have no evidence that paroxysmal tachycardia, associated with fibrillation of the auricles, reacts to drugs in any way differently from the type without fibrillation. I shall therefore consider paroxysmal tachycardia as a single therapeutic problem later.

(*e*) *In Cases with Paroxysmal Dyspnea.*—In one other type of case I have seen digitalis fail completely, in spite of the existence of rapid

action and fibrillation. That is, where the picture is dominated by severe paroxysms of dyspnea and eventual lung infarcts. Autopsy on a recent, peculiarly instructive case of this kind showed extensive coronary artery disease, with infarction of the heart-wall and intracardiac thrombi as a source of pulmonary embolism. The severity of the lesion of the myocardium in such a case seems adequate explanation for the failure of any drug. The caffein derivatives were equally without effect in this patient.

(*f*) *In Cases with Active Endocarditis.*—It is likewise evident that failure to respond to digitalis on the part of a heart the seat of active inflammatory processes, as in subacute and chronic septic endocarditis, can in nowise be expected, even though fibrillation exists. In my experience, a number of the cases of mitral disease in young persons, in which treatment has been of no benefit, have belonged to this category, the disease being a progressive one.

IV. DRUGS IN CARDIAC INSUFFICIENCY WITH NORMAL RHYTHM

A. *In Hypertensive Cases.*—When we turn to hearts beating under the influence of the normal pacemaker, the effects of treatment are, as a rule, much less prompt. For this reason it is more difficult to apportion correctly the credit for benefit produced among the varying factors entering into treatment. The influence of prolonged rest, the dietetic régimen, psychic factors, must all be taken into account before concluding that any drug which has been administered has contributed largely to the result. Nevertheless, in certain cases with normal rhythm, I have seen digitalis followed by as speedy relief of symptoms as in fibrillating cases. This has been particularly true in patients with cardiac insufficiency secondary to prolonged high blood-pressure. This type of disease, considered by many as chronic nephritis, I look on, with Jores and Aschoff, from the standpoint assumed long ago by Gull and Sutton, as cases of primary sclerosis of the small arteries, the kidney being, as a rule, extensively affected, but sometimes escaping entirely.

(*a*) *Digitalis.*—When these patients develop the picture of chronic passive congestion of the viscera with edema, digitalis is as clearly indicated as it is in fibrillating mitral hearts. This is the condition called by Sahli *Hochdruckstaaung,* and my experience is in absolute accord with his, that danger from increase in the blood-pressure is purely fanciful. My cases have frequently shown a moderate fall in pressure with the onset of cardiac weakness; and I always welcome a rise of 20 or 30 mm. under digitalis as evidence of benefit, though the behavior of the pressure is quite too variable to permit of it being used as a guide. This standpoint finds corroboration in the work of Miller, Price, Burnet and Josué and Godlewski. It cannot be too strongly insisted on that dan-

gerous increase in blood-pressure from digitalis, as used in human beings, is a superstition without any basis of clinical fact. On the contrary, a moderate hypertension, up to perhaps 180 mm. mercury, is a common accompaniment of cardiac insufficiency from any cause. With the readjustment of the circulation under digitalis, the relief of dyspnea and anxiety, and the absorption of edema, the blood-pressure usually falls in a striking manner. Redistribution of blood from the venous to the arterial side of the circulation, not increased arterial and diminished venous pressures, is what digitalis therapy produces in human beings. I believe that these cases stand second to fibrillating mitral cases in the frequency with which one may ameliorate their symptoms by the digitalis series, and this often independently of the existence or non-existence of fibrillation. A recent report by Schrenck (from Krehl's clinic) shows equally striking success in such patients. The influence on the rate is, as a rule, not very marked, though some slowing may occur. Gallop rhythm has seemed to me rather to favor the action of the drug. Many of these patients have a relative mitral regurgitation, which complicates the mechanical circulatory defect.

In order to study more exactly the frequency of fibrillation in these cases and its relation to digitalis action, I have analyzed my records of 458 private patients with high blood-pressures, seen during the past nine years, about whom I could obtain information in June, 1912. Two hundred and thirteen of these patients have died, 57 of chronic myocardial insufficiency. At the time of my examination, 71 had evidences of cardiac incompetency, but only 8 (11.2 per cent.) had perpetual arrhythmia, of whom 4 responded well to digitalis. Six patients with normal rhythm reacted to the drug equally well, 2 of them brilliantly. Of the 246 patients still living, 25 had insufficient hearts when seen, only 2 (8 per cent.) with fibrillation. Such percentages, I feel sure, are below the frequency of fibrillation in mitral valvular disease with decomposition.

There is a possible difference in the type of disease and the reaction to treatment between the well-to-do and the laboring classes, as one may observe in other pathological conditions. An analysis of a group of my ward patients especially studied, shows 63 with insufficient hearts, of whom 24 had fibrillation at some time. Of these 24, only 7 were patients with nephritis and hypertension uncomplicated by valvular disease; of these, 5 responded to digitalis. Of 12 regular hearts with hypertension, 5 were given digitalis, and only one showed improvement. However, among 75 patients with auricular fibrillation studied electrocardiographically by Dr. Stuart Hart at the Presbyterian Hospital, only 14 had a blood-pressure above 180 mm. Hg.

In many of these patients, therefore, we cannot attribute the good effect from digitalis to its action on the rate or rhythm, but I am forced to believe that we see in them the ventricular effects, the increase in completeness of systole at the existing blood-pressure. In addition, it is quite possible that the rapid diuresis and absorption of edema occasionally seen are due to the direct vasodilator effect of the drug on the renal arterioles. It is possible also that splanchnic vasoconstriction with a redistribution of the blood, such as digitalis is able to effect in animal experiments, takes place. In any event, the phenomena bear striking witness to wide-spread action on the circulation as a whole, and cannot be interpreted, as in rapid, irregular mitral hearts, merely to the control of rate and rhythm. I have seen a patient of this type who was waterlogged and who had been having nights of suffering in spite of large doses of morphin for weeks, sleep comfortably in three days after taking 2 drams of infusion of digitalis (60 c.c.) every four hours. His dyspnea was relieved and marked diuresis occurred; the edema was completely absorbed in a week; the enlargement of the liver disappeared, and he was able to walk with comfort. He had complete relief for three months.

I should not like to be understood as maintaining that the benefit from digitalis in auricular fibrillation is obtained without any effect on the ventricle other than that depending on the reduction in rate, but only that the latter is the demonstrable and principal effect. Into the underlying, fundamental problem as to why digitalis so much more easily affects rate and rhythm in fibrillating than in non-fibrillating hearts, I cannot enter. It is at the moment the most important problem awaiting solution by the pharmacologists.

(*b*) *Caffein and Allies.*—When digitalis alone does not effect prompt improvement in such patients, the caffein diuretics come in as valuable aids. I believe that their chief effect is local, on the kidney circulation. If given intermittently in comparatively small doses, 2 gr. of caffein, 10 of diuretin or 3 of theocin, for three doses, and not repeated until one or two days have elapsed, according to the method of Romberg's clinic, they are capable of producing remarkable increase in urinary output, with absorption of edema, not only in cardiac and renal disease, but occasionally even in the ascites of cirrhosis of the liver. The work of Schlayer and the recent work of Mosenthal and Schlayer,[1] have shown how overdosage of these drugs may reverse the effect on the vessels and result in oliguria. I lay great stress on the method I have outlined as a factor in the success that may be achieved with these purin diuretics.

Besides their effect on the kidney, however, their action in combination with digitalis in certain cases suggests that their well-known

1. Personal communication; will be published shortly.

property of dilating the coronary arteries may be of therapeutic importance. Braun has recently given an experimental basis for combined digitalis-caffein therapy, and I have a number of case histories which bear testimony to its value. That caffein can ever supplant digitalis in those circulatory diseases in which digitalis is indicated, I do not believe. Miller's interesting study of decompensated nephritic hearts has shown that relief of dyspnea is much more striking with digitalis; theophyllin, on the other hand, produced marked diuresis in many cases, without notably lessening the respiratory distress.

B. *In Primary Myocardial Insufficiency.*—This condition, without notable increase in pressure, dependent on coronary sclerosis or degenerative muscle changes, may, if it presents the clinical picture of chronic passive congestion and edema, respond to the digitalis bodies. But, again, many cases fail to respond, and it is in these patients particularly that I have seen the undesirable effects of digitalis on the heart rhythm. Such effects are heart block, which in the two cases reported by Taussig, was permanent and serious, but which may be beneficial, as in a case reported by Hewlett; fibrillation, which may then be favorably affected by digitalis; extrasystoles and bigeminal rhythm, which in these cases are usually undesirable, and the *pulsus alterans.* In a recent case of this type I have seen *pulsus alterans* regularly produced after digitalis had been given for a few days, and the patient regularly made worse by it. When these patients are refractory to the digitalis drugs, combined digitalis-caffein medication must be tried, or one of the caffein series alone, but the likelihood of benefit is not great. For their paroxysms of dyspnea, nitroglycerin or other nitrite vasodilators may give temporary relief or cut short the attack. In acute edema of the lungs, as seen in such patients, I believe nitroglycerin to be of real service; and caffein hypodermically also helps.

C. *In Mitral Disease with Regular Rhythm.*—Here, again, drugs rarely act as in the fibrillating cases. Some of these cases, as a number reported by Mackenzie, improve slowly under digitalis, without showing any effect on the heart-rate. In others, sinus arrhythmias, extrasystoles, block, and even *pulsus alterans* may be produced, accompanied by improvement in some, and not in others. The French clinicians have always held to the value of caffein in these cases, but I have not been convinced of it. Improvement is usually so slow that doubt must exist as to the value of any drug used; but digitalis up to toxic symptoms does seem to improve the dyspnea.

D. *In Aortic Disease.*—The use of cardiac drugs in aortic disease, aortic insufficiency especially, has been much fought over. Corrigan's dictum that digitalis should never be given has held sway in many minds. I cannot agree with this. In a number of instances I have seen marked

and lasting benefit from digitalis in aortic insufficiency, where the clinical picture was that of chronic passive congestion and edema. The French have spoken of this as the mitral stage of aortic regurgitation, and a relative mitral regurgitation is a frequent accompaniment. Huchard held that aortic incompetency was no contra-indication to digitalis. Schrenck reports its successful use in seven out of nine cases. Romberg does not favor it in uncomplicated cases. The frequent failure, and occasional sudden death, seen during its use in aortic insufficiency, were formerly laid to slowing of the heart with attendant increase in the regurgitation during diastole. If the drug is properly used and large doses avoided, however, marked slowing does not occur.

Sahli explains the failure by assuming that aortic hearts do not produce serious symptoms, as a rule, until the mechanical defect has become very extreme. Failure is then rapid. So far as the symptoms which he means are those of general venous stasis, this assumption seems warranted.

Another factor, I believe, may be of predominant importance, namely, that most aortic regurgitation is not a chronic stationary valvular defect, but the result of a progressive disease, syphilitic aortitis, frequently associated with dilatation of the arch and with actual aneurysm. The symptoms in these cases are rarely those of venous congestion. The striking symptoms are paroxysmal in nature, anginoid pain, and attacks of intense dyspepsia. Sudden death, with or without treatment, is common. This is not the type of circulatory disorder in which digitalis can be expected to do good, and I believe that many of the sudden deaths attributed to digitalis are due to the disease itself. Apart from the treatment of these cases with salvarsan, the paroxysms often yield promptly to one of the nitrites. This condition and its treatment have recently been well studied by Longcope. I find that Hoffmann also shares my view that much of the failure of digitalis in such patients is dependent on the nature of the underlying disease. One should also remember the frequent involvement of the coronary arteries in this condition.

So far as the favorable action of digitalis in some cases of aortic insufficiency is concerned, it seems as though the so-called diastolic effects, the increased diastolic distensibility first described by Williams, and recently studied by Werschinin and by W. Straub, as his so-called "pure negative" effect, would be the action most to be desired, or a combination of this with increased completeness of systole. The production of this type of effect experimentally seems largely a function of the dosage. Such great precision of dosage is at present clinically impossible, but it seems not too much to hope that through the intravenous administration of strophanthin or pure digitalis glucosides, it may in the future be possible to arrive at the actual production of this or other

especially desired effects. Zollinger's experiments on rabbits with artificially produced aortic regurgitation have shown a greater efficiency of the heart, with some increase in the diastolic filling, under digitalis.

E. *In Failure of the Right Ventricle.*—In the comparatively rare cases of isolated failure of the right ventricle, secondary to advanced emphysema, kyphoscoliosis, and so forth, digitalis is notoriously unsuccessful. In such cases, the dyspnea is dependent as much on the primary disease in the lung as on the cardiac weakness, and therefore cannot be relieved. In addition, as in so many cases of primary myocardial weakness, in aortic disease, and in some of the mitral hearts with normal rhythm, the eventual appearance of general venous congestion is the last stage in a slowly developing disproportion between the ventricular muscle and the demand it is called on to meet. The reserve force of the heart, particularly of the right ventricle, is not unlimited. Where sudden overstrain, or the sudden development of fibrillation upsets the balance, the removal of this additional interference with proper cardiac function may give prompt relief. Where no such deleterious factor enters, we must look on the functional exhaustion as the expression of anatomical lesions so extreme as to be analogous to the surgeon's category of "inoperable cases," and not blame our remedies for failure to help. When in emphysema, the occurrence of an attack of asthma on the other hand leads to acute insufficiency of the right ventricle, I believe from my experience that caffein often acts surprisingly well. Meyer endorses this view.

F. *In Exophthalmic Goiter.*—In the rapid heart of exophthalmic goiter I have not personally seen any definite effects from digitalis, except when the heart became markedly insufficient, with chronic passive congestion and edema. Then I have known it to act admirably. I have at times thought that the earlier cases were improved by continued small doses of digitalis or strophanthus, but with our present knowledge of the cardiac rhythm, I do not feel that the evidence I accepted can be relied on, and that improvement was not due to other therapeutic measures, mainly rest.

Overdosage.—In all these hearts with regular rhythm I believe that dosage should be more cautious than in the fibrillating hearts. The onset of abnormal rhythm is one guide to toxic effects. Another, which I have always heeded, is the sudden cessation of a previous diuresis. Withering himself made this a guide, and many experienced clinicians have found it of value (Meyer).

V. DRUGS IN OTHER DISTURBANCES OF RHYTHM

A. *In Paroxysmal Tachycardia.*—Practically the same considerations exist in paroxysmal tachycardia. Here it is perfectly clear that we do not possess any drug with which we can definitely cut short the

paroxysm. I am in agreement with Vaquez that no form of digitalis treatment is indicated, except in very protracted attacks, when evidences of cardiac insufficiency appear, and that then intravenous strophanthin is probably the best form. That in the case cited by Edens, a patient with severe mitral disease as well, who received digitalis for five days without effect and on the sixth had a sudden fall of the rate to one-third, the result can be attributed to the drug taken, is to me most unlikely. The failure even of fibrillating paroxysmal tachycardia to respond to digitalis is one of the most difficult problems awaiting solution in this field. It shows plainly that fibrillation itself is not the sole condition determining the beneficial results of digitalis therapy. It is to be hoped that careful electrocardiographic studies of the effects of large doses of strophanthin intravenously in such attacks will shed light on the present insoluble difficulties.

B. *In Heart Block.*—The use of cardiac remedies in heart block is a subject about which much apprehension exists, largely because of theoretical considerations. In complete block the inhibitory effects of digitalis are not to be feared, and, as von Tabora's experiments have shown, it is even possible that the idioventricular rhythm may be increased by it. When cardiac insufficiency with venous stasis supervenes on complete block, digitalis is definitely indicated. Like Vaquez and Edens, I have seen great improvement following its use. As Edens remarks, in such cases one can scarcely escape the conclusion that one has observed clinically the definite systolic effects of digitalis. In partial block, Volhard has seen reassociation occur under digitalis; but complete block is so likely to result that it should be experimented with cautiously. I have recently observed such reassociation follow the use of theobromin.

C. *In Extrasystolic Irregularity.*—The treatment of extrasystolic irregularities is a subject of such complexity at the present time that consideration of it does not seem to me profitable. Certain types are improved by digitalis, as Edens has shown; others may be made worse. Frequent extrasystoles in insufficient hearts always seem to me an indication for caution in the use of digitalis remedies.

VI. DRUGS IN ANGINA PECTORIS

Closely allied to the symptom-complex presented by many cases of aortic regurgitation, is angina pectoris. Anginoid pain on exertion is evidence of an abnormal function response on the part of the heart, totally different from the syndrome of chronic passive congestion and edema. I believe that the use of the terms "myocardial insufficiency" or "asystole" should be restricted to hearts exhibiting the latter. The lack of a satisfactory theory to explain the mechanism of anginoid pain

forces us to rely on clinical experience as a guide to its treatment. My experience, through my association for a number of years in the consulting office of my father, among a class of patients often afflicted with this condition, has given me the opportunity to observe the effect of treatment in many hundreds of such patients. There is not the slightest doubt in my mind that in anginoid pain on exertion, or excitement, which must not be identified completely with the intense, and often fatal, paroxysms of severe angina pectoris, the quickly acting nitrites are the sovereign and almost invariably effective remedies for the relief of the paroxysm. What is more, one may even observe that nitrites administered just before exertion is undertaken will frequently enable these patients to perform double the amount of work of which they would be otherwise capable, and without pain. My preference is for nitroglycerin, which patients can carry with them in fresh tablet form. The tablets must be taken on the tongue, not swallowed. The absorption of nitroglycerin from the mouth takes place as a rule in less than one minute; from the stomach it is much more variable and delayed. Many failures to obtain relief in anginoid pain with nitroglycerin are due to inert drugs, or to the drug being swallowed. Amyl nitrite I do not think is any more effective; it is objectionable because of the odor and the attention this attracts to the patient. All other nitrites act too slowly. In the angina of hypertensive cases, nitroglycerin is peculiarly effective, but it frequently acts well in apparent coronary angina associated with low pressure, and also in the anginal attacks of syphilitic aortitis. In some of these patients very large doses, up to 1/10 grain or more, may be necessary; and the dose is always a matter for individual experiment. The continued administration of the nitrites I do not believe has any great value. From the observation of the blood-pressure during such paroxysms, my feeling is strong that the nitrites do not give relief through their lowering of the aortic blood-pressure, for the relief usually precedes this. I am inclined to regard their favorable action as due to local dilatation of the coronary arteries, though of this one cannot be certain. My personal experience, which is in accord with that of Huchard and of Krehl, is that the continued administration of iodid in small doses is of more value in diminishing the frequency of the paroxysms than any other remedy.

In very severe angina pectoris the nitrites are clearly valueless, and morphin is the strict indication. Here it is possible that digitalis may support the heart, as some of Miller and Matthews' experiments on ligature of the coronary arteries seem to demonstrate. When anginal attacks are followed by dilatation of the heart and myocardial insufficiency of the ordinary type, the attacks regularly disappear. Under such circumstances I have had brilliant results with digitalis, as in any

other type of insufficient heart. An interesting observation, which has been made by Musser, is that recovery from the ventricular insufficiency under digitalis is frequently followed by recurrence of anginal pain. One is strongly tempted here to believe that the alteration in tone of the wall of the ventricle has been the factor. I have not seen striking results from the use of theobromin as advocated by Askanazy.

VII. THE TREATMENT OF RECENT ENDOCARDITIS AND INITIAL CARDIAC INSUFFICIENCY

The use of digitalis in the very earliest stages of cardiac insufficiency has been urged by Hoffmann and Fraenkel (cited by Meyer), and especially by Romberg. I am inclined to believe in the cautious, persistent use of small doses after convalescence from acute rheumatic endocarditis, in conjunction with physical methods of treatment; but I do not feel certain of the part that digitalis plays in bringing about improvement. In the slight myocardial weakness of obese persons, of anemia, and of convalescence from severe acute illness, I doubt its usefulness. In the earlier stages of decompensation and valvular disease, without fibrillation, I believe the continued use of small doses is ordinarily desirable, not pushing to the point of producing disturbances of rhythm; but until we have better means for measuring the effects of digitalis on other functions than rhythm, scepticism of clinical evidence of improvement in such cases is perfectly legitimate.

A. *Circulatory Failure of Acute Infectious Disease.*—The treatment of the circulatory failure of acute infectious disease must recognize the predominant part played by the vasomotor system, rather than the heart, in the production of the clinical picture. The clinical syndrome, the usual failure of the pure cardiac remedies, and the experimental demonstrations of Romberg and Pässler show this. Our means of combating extreme vasomotor depression are limited. The ideal drug would be a substance acting like epinephrin, but whose effects were persistent. Such a substance we do not possess. I have seen the most amazing restoration from apparent imminent death follow the intravenous injection of epinephrin in large doses—in one case over 4 c.c. of the 1 to 1,000 solution in a little more than an hour. This was in a case of extensive bronchopneumonia, with extreme cyanosis. Life was prolonged for three days. Only in pneumonia, however, is the fleeting action of epinephrin likely to be of service. Caffein has seemed to me of benefit. Camphor is little used in America. Recent experience at the Rockefeller Institute would seem to indicate that large doses of strophanthin, to the point of toxic effects, may occasionally save life in pneumonia with circulatory failure attended by extreme tachycardia. These experiments have been conducted by Dr. Fraser under absolute electrocardiographic

control; they will not be published until they are confirmed in a group of cases. The possibilities of danger are considerable, but it is to be hoped that the very thorough studies being carried on will yield a valuable and rational method of treatment. I am quite sure that in these cases digitalis by mouth is worthless, and have myself formerly been in the habit of employing it subcutaneously, which is always painful. I do, however, recognize cases in which the combination of subcutaneous digitalis and caffein has seemed to give clear clinical evidence of combating the circulatory collapse. In so protracted a disease as typhoid fever, I do not believe drugs have any value. As to the efficiency of strychnin, except as a respiratory stimulant, I am in doubt. To be of use, it certainly must be given in large doses.

VIII. CONCLUSIONS

Such a review of the comparative clinical value of cardiac remedies shows how very real has been the progress of pharmacology and therapeutics during recent years. The indications for digitalis therapy have become increasingly precise through the exact study of the cardiac rhythm. One task for the future is the elaboration of equally accurate clinical methods for the estimation of the more fundamental effects of these drugs on the ventricle, and for the analysis of their cardiac and vasomotor actions. That increasing fineness of observation can ever replace the skill and experience of the master clinician, I do not for a moment believe. Withering, depending only on his unaided sight and touch, laid down the main rules for digitalis therapy which we follow to-day. The treatment of disease is an art which will ever require greater practice to master its increasingly elaborate technic, and riper judgment to utilize the growing volume of exact analytical data which scientific methods of clinical observation are furnishing. Methods can never replace the master.

BIBLIOGRAPHY

Agassiz, C. D. S.: Observations upon the Effects of Strophanthin in Cases of Auricular Fibrillation, Heart, 1911-12, iii, 353.

Askanazy, A.: Klinisches über Diuretin, Deutsch. Arch. f. klin. Med., 1896, lvi, 209.

Bailey, Harold C.: A Clinical Study of Crystalline Strophanthin, Jour. Pharmacol. and Exper. Therap., 1909, i, 349.

Boos, W. F., Newburgh, L. H., and Marx, H. K.: The Use of Digipuratum in Heart Disease, The Archives Int. Med., 1911, vii, 551.

Braun, Ludwig: Die Experimentelle Grundlage der Digitalis-Caffein-Medication, Ztschr. f. exper. Path. u. Therap., 1905, i, 360.

Brunton, Lauder: Therapeutics of the Circulation, Phila., 1908, Blakiston's Son & Co., p. 145.

Burnet, J.: Effect of Certain Cardiac Remedies on Arterial Pressure, Med. Press and Circular, 1912, xciv; Abstr., Jour. Am. Med. Assn., 1912, lix, 1222.

Busquet, H.: Action cardiaque comparée de l'extrait physiologique de digitale et des autres préparations digitaliques, Compt. rend. Acad. d. Sc., 1912, clv, 509; Abstr., Ztschr. f. Chemotherap., part 2, 1912, i, 1215.

Chauffard, A., and Troisier, Jean: Effets utiles et dangers des injections de strophanthine, Bull. et Mém. Soc. méd. d. hôp., Paris, 1909, xxvii, 700.

Cloetta, M.: On Digalen, Münch. med. Wchnschr., 1904, xxxiii; Ueber den Einfluss der chronischen Digitalisbehandlung auf das normale und pathologische Herz, Arch. f. exper. Path. u. Pharmakol., 1908, lix, 209.

Cow, Douglas: Notes on some New Substitutes for the Galenical Preparations of Digitalis, Biochem. Jour., 1912, vi, 219.

Cushny, A. R.: The Therapeutics of Digitalis and its Allies, Harvey Lectures, 1910-1911, Phila., J. B. Lippincott, p. 46; Treatment of Non-valvular Heart Disease, Brit. Med. Jour., Sept. 21, 1912, 685.

Cushny, A. R., Marris, H. F., Silberberg, M. D.: The Action of Digitalis in Therapeutics, Heart, 1912, iv, 33.

Danielopolu, D.: Recherches sur l'action de la strophantine en injection intravéneuse dans les affections du coeur, Arch. d. mal. du coeur, 1908, i, 624.

Danielopolu, D., Dumitrescu, A., Popescu: La constante uréo-sécrétoire chez les cardiaques asystoliques. Action de la digitale, Compt. rend. Soc. de Biol., 1913, lxxiv, 295.

Dixon, W. E.: Critical Review. The Digitalis Preparations employed in Medicine, Quar. Jour. Med., 1911, v, 297.

Edens, E.: Ueber Digitaliswirkung, Deutsch. Arch. f. klin. Med., 1911, civ, 512.

Edmunds, C. W., and Hale, W.: The Physiological Standardization of Digitalis, Bull. Hyg. Lab., U.S.P.H.S., 1908, No. 48.

Eggleston, Cary: Clinical Observations on the Duration of Digitalis Action, Jour. Am. Med. Assn., 1912, lix, 1352.

Fahrenkamp, Carl: Ueber die verschiedene Beeinflussung der Gefässgebiete durch Digitoxin, Arch. f. exp. Path. u. Pharmakol., 1911, lxv, 367.

Focke: Ueber den gleichmässigen Wirkungswert von gut präpariertem und gut aufbewahrtem Digitalispulver, Therap. d. Gegenw., 1904, vi (N. F.); 250.

Fraenkel, Albert: Chronische Herzinsuffizienz und intravenöse Strophanthintherapie, Münch. med. Wchnschr., 1912, lix, 289; Bemerkungen zur internen Digitalismedikation. Arch. f. exp. Path. u. Pharmakol., 1907, lvii, 131; Ueber Digitalistherapie, Ergeb. d. inn. Med. u. Kinderh., 1908, i, 68; Zur Frage der Kumulation, insbesondere beim Digalen, Arch. f. exp. Path. u. Pharmakol., 1907, lvii, 123.

Fraenkel, A., and Schwartz, G.: Ueber Digitaliswirkung an Gesunden und an kompensierten Herzkranken, Arch. f. exp. Path. u. Pharmakol., 1908, lix, 188; Ueber intravenöse Strophanthininjektionen bei Herzkranken, Arch. f. exp. Path. u. Pharmakol., 1907, lvii, 79.

Gelbart, Moses: Ueber den Einfluss der Digitalis auf frisch entstandene Klappenfehler, Arch. f. exp. Path. u. Pharmakol., 1911, lxiv, 167.

Gibson, Alexander G.: A Contribution to the Knowledge of the Action of Digitalis on the Human Heart, Quar. Jour. Med., 1907-8, i, 173.

Gottlieb, R.: Ueber Herzmittel und Vasomotorenmittel, XIX Kongr. f. inn. Med., 1901, 21; Haben therapeutische Digitalisgaben Gefässwirkung? Therap. Monatsch., 1912, xxvi, 479.

Gottlieb, R., and Magnus, R.: Ueber die Gefässwirkung der Körper der Digitalisgruppe, Arch. f. exp. Path. u. Pharmakol., 1902, xlvii, 135.

Gottlieb, R., and Ogawa, S.: Ueber die Resorption von Digitoxin aus Digitalispräparaten und über ihre Beziehung zu Wirkung und Nebenwirkungen derselben, München. med. Wchnschr., 1912, lix, 2265, 2339.

Gottlieb, R., and Tambach, R.: Ueber Digipuratum, München. med. Wchnschr., 1911, lviii, 10.

Hale, W.: Digitalis Standardization and the Variability of Crude and of Medicinal Preparations, Bull. Hyg. Lab., U.S.P.H.S., 1911, No. 74.

Hare, H. A., and Coplin, W. M. L.: The Influence of Digitalis on the Heart Muscle When the Drug is Administered for a Long Time, Therap. Gaz., Detroit, 1897, xxi, 800.

Hartung, C.: Ueber Digifolin, ein neues Digitalispräparat, München. med. Wchnschr., 1912, lix, 1944.

Hatcher, Robert A.: The Absorption, Excretion, and Destruction of Strophanthin, Am. Jour. Physiol., 1909, xxiii, 303; The Persistence of Action of the Digitalins, THE ARCHIVES INT. MED., 1912, x, 268; Note on Strophanthin, Jour. Am. Med. Assn., 1910, liv, 1050.

Hatcher, Robert A., and Bailey, Harold C.: Tincture of Strophanthus and Strophanthin, Jour. Am. Med. Assn., 1909, lii, 5; The Clinical Use of Strophanthus, Jour. Am. Med. Assn., 1910, lv, 1697.

Hatcher, Robert A., and Eggleston, Cary: The Emetic Action of the Digitalis Bodies, Jour. Pharmacol. and Exper. Therap., 1912, iv, 113.

Hedinger, Max: Uber die Wirkungsweise von Nieren- und Herzmitteln auf kranke Nieren, Deutsch. Arch. f. klin. Med., 1910, c, 305; Ueber die Wirkungsweise von Nieren- und Herzmitteln bei nierenkranken Menschen, München. med. Wchnschr., 1912, lix, 1098; Experimentelle Studien über die Wirkungsweise von Nieren- und Herzmitteln auf kranke Nieren, Kongr. f. inn. Med., 1910, xxvii, 750.

Henrijean, F.: Traitement de la bradycardie par la digitale, Congr. de Méd., 1910; Abstr., Arch. d. mal. du coeur, 1910, 740.

Heubner, W.: Das Wesen der Digitaliswirkung, Therap. Monatsch., 1912, xxvi, 157.

Hewlett, Albion W.: Heart Block in the Ventricular Walls, THE ARCHIVES INT. MED., 1908, ii, 139.

Hewlett, Albion W., and Barringer, T. B.: The Effect of Digitalis on the Ventricular Rate in Man, THE ARCHIVES INT. MED., 1910, v, 93.

Hochheim, K.: Klinisches und Experimentelles über g-Strophanthin Thoms, Centralbl. f. inn. Med., 1906, xxvii, 65.

Hoffmann, August: Funktionelle Diagnostik und Therapie der Erkrankungen des Herzens und der Gefässe, Wiesbaden, 1911, J. F. Bergmann, p. 406.

Holste, Arnold: Ueber die Bestimmung des pharmakologischen Wirkungswertes der Blätter von Digitalis purpurea, Arch. f. exp. Path. u. Pharmakol., 1911, lxvi, 161.

Huchard, H.: Les maladies du coeur et leur traitment, Paris, 1908, J. B. Baillière et fils.

Janeway, Theodore C.: The Use and Abuse of Digitalis, Am. Jour. Med. Sc., 1908, cxxxv, 781.

Jonescu, D., and Loewi, O.: Ueber eine spezifische Nierenwirkung der Digitaliskörper, Arch. f. exp. Path. u. Pharmakol., 1908, lxix, 71.

Josué, O., and Godlewski, Henri: Pression artérielle et digitaline, Bull. et mém. Soc. méd. d. hôp., 1912, xxviii, 480.

Kasztan, Max: Beiträge zur Kenntnis der Gefässwirkung des Strophanthins, Arch. f. exp. Path. u. Pharmakol., 1910, lxiii, 405.

Kauffmann, Rudolf: Ueber den Einfluss des Schmerzes und der Digitalis auf die Herzarbeit des normalen Menschen, Ztschr. f. exp. Path. u. Therap., 1913, xii, 165.

Kobert, R.: Ueber die wirksamen Bestandteile und die Verordungsweise der Digitalis, München. med. Wchnschr., 1912, lix, 1864.

Krafft, F.: Die Glykoside der Blätter von Digitalis purpurea, Arch. d. Pharmakol., 1912, ccl. 118; Abstr., Therap. Monatsch., 1912, xxvi, 822.

Krehl, L.: Diseases of the Myocardium and Nervous Diseases of the Heart, in Nothnagel's *Practice of Medicine*, Am. ed., Phila., W. B. Saunders, 1908, p. 543.

Laslett, E. E.: Sinus Arrhythmia of High Grade Induced by Digitalin, Quart. Jour. Med., 1911, v, 377.

Lewis, Thomas: The Reaction of the Heart to Digitalis When the Auricle is Fibrillating, Brit. Med. Jour., 1910, Nov. 20, 1670; Auricular Fibrillation and

its Relation to Clinical Irregularity of the Heart, Heart, 1909-10, i, 306; Observations upon Disorders of the Heart's Action, Heart, 1911-12, iii, 279.

Lewy, Benno: Die Arbeit des gesunden und des kranken Herzens, Ztschr. f. klin. Med., 1897, xxxi, 520.

v. Lhota, C. L.: Untersuchungen über das Verhalten der Digitalisstoffe im Körper, besonders bei der Angewöhnung an dieselben, Arch. internat. de Pharmacol., 1912, xxii, 61; Abstr., Therap. Monatsch., 1912, xxvi, 890.

Longcope, W. T.: Syphilitic Aortis: Its Diagnosis and Treatment, THE ARCHIVES INT. MED., 1913, xi, 15.

Mackenzie, James: Digitalis, Heart, 1910-11, ii, 273; General Treatment of Diseases and Affections of the Heart, in A System of Treatment, ed. by Arthur Latham and T. C. English, London, 1912, J. and A. Churchill, pp. 1194-1254.

Meyer, Arthur W.: Die Digitalis-Therapie, Jena, Gustav Fischer, 1912.

Meyer, Felix: Hat g-Strophanthin eine Einwirkung auf den Koronarkreislauf?, Med. Klinik, 1912, viii, 869.

Miller, Jos. L.: Some Clinical Observations on the Drug Treatment of Edema, Tr. Assoc. Am. Phys., 1912, xxvii, 137; Am. Jour. Med. Sc., 1912, cxliv, 8.

Miller, Jos. L., and Matthews, S. A.: Preliminary Report on Experimental Ligation of the Coronary Arteries, Tr. Assoc. Am. Phys., xxiii, 83.

Musser, John H.: Angina Pectoris: Its Relation to Dilatation of the Heart, Tr. Assoc. Am. Phys., 1897, xii, 70.

Ogawa, S.: Ueber die Resorption wirksamer Bestandteile aus Digitalisblättern und Digitalispräparaten, Deutsch. Arch. f. klin. Med., 1912, cviii, 554.

Pratt, J. H.: On the Importance of Determining the Potency of Digitalis Preparations, Bost. Med. and Surg. Jour., 1910, clxiii, 279.

Price, F. W.: Some Investigations of the Action of Digitalis on the Blood-Pressure in Man, Brit. Med. Jour., 1912, Sept. 21, 689.

Rihl, J.: Analyse von fünd Fällen von Ueberleitungsstörungen, Ztschr. f. exp. Path. u. Therap., 1905, ii, 83.

Romberg, Ernst: Ueber Digitalis, München. med. Wchnschr., 1913, lx, 1.

Romberg, E., und Pässler, H.: Experimentelle Untersuchungen über die allgemeine Pathologie und Therapie der Kreislaufsstörung bei akuten Infektionskrankheiten, Deutsch. Arch. f. klin. Med., 1899, lxiv, 652.

Sahli, H.: Ueber Herzmittel und Vasomotorenmittel, XIX Kongr. f. inn. Med., 1901, 45.

Schlayer: Ueber die Ermüdbarkeit der Nierenfunktion, XXIX Kongr. f. inn. Med., 1912, 500.

Schlayer und Hedinger: Experimentelle Studien über toxische Nephritis, Deutsch. Arch. f. klin. Med., 1907, xc, 1.

Schmiedeberg, O.: Untersuchungen über die Bestimmung des pharmakologischen Wirkungswertes der getrockneten Blätter von Digitalis purpurea, Arch. f. exp. Path. u. Pharmakol., 1910, lxii, 305.

Schrenk, Theophil: Ueber die Wirkung der Digitalis auf die verschiedenen Formen von Herzerkrankung, München. med. Wchnschr., 1912, lix, 2908.

Straub, Walther: Dynamik des Froschherzventrikels bei nichttödtlicher Digitalisvergiftung, Ztschr. f. exp. Path. u. Pharmakol., 1905, i, 489.

Tabora, von: Ueber die experimentelle Erzeugung von Kammersytolenausfall und Dissociation durch Digitalis, Ztschr. f. exp. Path. u. Therap., 1906, iii, 499.

Taussig, Albert E.: Complete and Permanent Heart-block following the Use of Digitalis in Auricular Fibrillation, THE ARCHIVES INT. MED., 1912, x, 335.

Vaquez, H.: Les arythmies, Paris, Baillière, 1911.

Vaquez et Leconte: Les injections intraveineuses de strophanthine dans le traitement d l'insuffisance cardiaque, Bull. et. mém. Soc. méd. d. hôp, Paris, 1909, xxvii, 662.

Veiel, E.: Ueber Digipuratum Knoll, München. med. Wchnschr., 1910, lvii, 2046.

Volhard, F.: Ueber die Beziehungen des Adams-Stokes'schen Symptomenkomplexes zum Herzblock, Deutsch. Arch. f. klin. Med., 1909, xcvii, 348.

Weis, Edmund: Ueber den physiologischen Wirkungswert einiger Digitalispräparate, Osterr. Sanitätswesen, 1912, xxiv, Beilage, 162; Abstr., Therap. Monatsch., 1912, xxvi, 662.

Werschinin, N.: Zur Kenntnis der diastolischen Herzwirkung der Digitalingruppe, Arch. f. exp. Path. u. Pharmakol., 1909, lx, 328.

Williams, Francis: Ueber die Ursache der Blutdrucksteigerung bei der Digitalinwirkung, Arch. f. exp. Path. u. Pharmakol., 1881, xiii, 1.

Windle, J. Davenport: Heart-block from Drugs of the Digitalis Group, Heart, 1911-12, iii, 1.

Wynn, Frank B.: Will the Long-continued Administration of Digitalis induce Cardiac Hypertrophy? Jour. Am. Med. Assn., 1904, xliii, 164.

Zollinger, Fr.: Zur experimentellen Pathologie und Therapie der akuten Aorteninsuffizienz, Arch. f. exper. Path. u. Pharmakol., 1909, lxi, 193.

INTERPRETATION OF THE AUSCULTATORY BLOOD-PRESSURE SOUNDS *

D. R. HOOKER, M.D., AND J. D. SOUTHWORTH, B.A.
BALTIMORE

The auscultatory method for the determination of arterial blood-pressure in man, described by Korotkoff in 1905,[1] has called forth numerous papers particularly from those making a clinical application of the method. There appears to be unanimity of opinion that the systolic pressure is established with the onset of the brachial sound during the fall of proximal constricting pressure, but the point of diastolic pressure, originally established by Korotkoff as coincident with the disappearance of all sound, has been variously interpreted.

In a recent paper by Taussig and Cook,[2] the literature is fully presented. These authors establish the diastolic pressure at the fourth phase in the production of the sound; that is, at the point at which, during the fall of constricting pressure, the sound changes from sharp to dull, a change which is generally recognized to occur in normal subjects just before the cessation of sound. Warfield, Hoover and Dehio support the same belief. Without intentional disregard therefore, of the writers who are in agreement with the original position taken by Korotkoff, it would seem that the balance of recent experimental evidence supports a less simple reading of diastolic pressure than the one set forth by Korotkoff. Our own results suggest, however, that the point of cessation of sound so closely approximates to the diastolic pressure that it serves all practical demands of clinical refinement. Indeed, not one of our sixteen records shows evidence of the continuation of the sound beyond the point of diastolic pressure.

METHOD

The object of our experiments was to record photographically the brachial sounds simultaneously with the records of systolic and diastolic pressures as given by the Erlanger apparatus.

We used the method of Einthoven and Geluk[3] for sound registration. An ordinary Bell telephone transmitter was placed in the primary circuit of an induction apparatus carrying a current of from 200 to 350 milliamperes. The mouthpiece of the telephone was replaced by a brass tube

* Submitted for publication Oct. 23, 1913.
* From the Physiologic Laboratory of the Johns Hopkins University.

1. Korotkoff, N. S.: Tr. Imp. Mil. Med. Acad., St. Petersburg, 1905, xi, 365.
2. Taussig and Cook: THE ARCHIVES OF INT. MED., 1913, xi, 542.
3. Einthoven and Geluk: Arch. f. d. ges. Physiol., 1894, 57, 617.

with an adjustable lateral opening. The brass tube was connected by about 10 cm. of rubber tubing to a similar piece of brass, which served for a stethoscope bell and was fastened with tape over the brachial artery just below the blood-pressure cuff at the bend of the elbow. The capillary electrometer was in the secondary circuit, and so placed with respect to a lantern that the movement of the magnified image of the capillary of mercury could be photographed on a moving sensitized film. The size of the lateral opening and the position of the secondary coil enable the observer so to adjust the apparatus that the capillary was stationary, except when a vascular sound was being produced beneath the stethoscope bell.

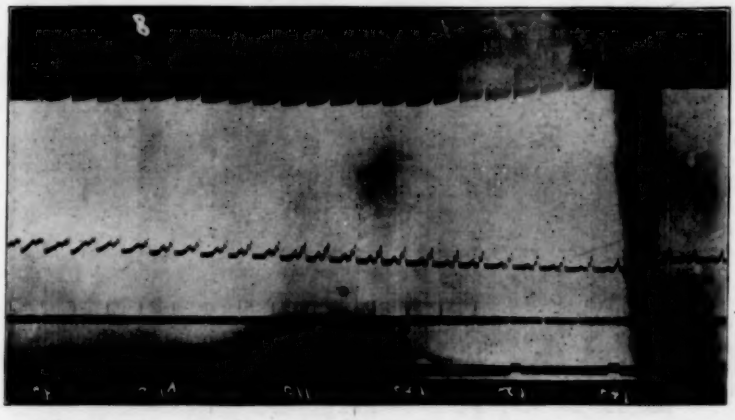

Fig. 1.—M. U. April 12, 1913. Narrow cuff. The reproduction is a mirror picture of the record. As in the following illustrations the first line shows the breaks in the shadow of the mercury capillary coincident to sounds over the brachial artery; the second line shows the pulse waves recorded by the Erlanger sphygmomanometer; the third line gives the time in seconds; the fourth line signals each 10 mm. Hg fall of pressure, the double signal marking 100 mm. Hg pressure in the constricting cuff. The record reads from right to left. It will be seen that the first sound coincides with the sudden increase of pulse magnitude (systolic pressure) and the last sound coincides with the sudden decrease of pulse magnitude (diastolic pressure).

Such adjustment is of very practical importance. It is obvious that the reliability of our results and the deductions made therefrom would be conditioned by the accuracy of the recording device employed. Such reliability would be of increased significance during the weak phases of the sound, namely, at the points of systolic and diastolic pressure. It was observed that the graphic record of sounds produced varied with the width of pressure cuff employed, but these variations corresponded with the Erlanger readings. We were finally convinced of the reliability and accuracy of our method when we attempted to apply it to the study of

similar sounds produced in a circulation schema. When this device was employed the instrument recorded air vibrations which could not be detected with the ear. In other words, the instrument was at least as delicate as the ear, a fact which established beyond a doubt in our minds that we were able to record accurately the sounds produced in the brachial artery. It will be noted, too, as further evidence of the accuracy of the method that the records of sound production and pulse magnitude change at the point of systolic pressure are in absolute agreement. If the sound registration were inaccurate we should expect disagreement in the two records at this point, since observers are united that this is the point of systolic pressure.

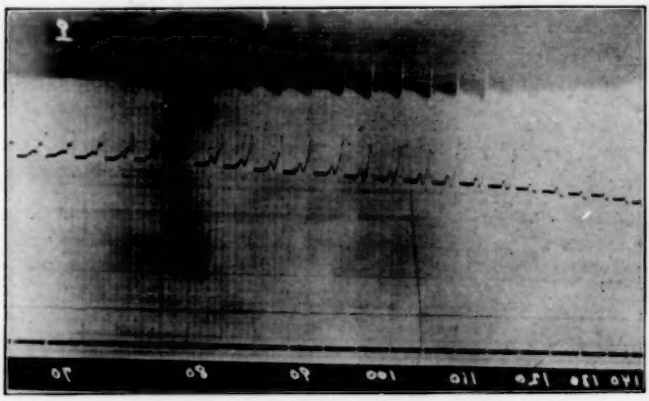

Fig. 2.—M. U. June 30, 1913. Broad cuff.

In addition to the movements of the capillary electrometer the records show (1) the shadow of the movements of the Erlanger recording lever; (2) the signal-key used to record the pressure in millimeters of mercury in the constricting cuff and (3) the time in seconds. The data thus gathered give us (1) the rate of the heart-beat; (2) the amount of constricting pressure; (3) the sudden increase in amplitude of movement of the Erlanger lever coincident with systolic pressure; (4) the sudden decrease in amplitude of movement of the Erlanger lever coincident with diastolic pressure, and (5) the relationship of the onset and disappearance of the brachial sound as shown by the shadow record of the mercury capillary to the systolic and diastolic arterial pressure as recorded with the Erlanger instrument.

The record of constricting pressure was obtained by closing a signal-key for each 10 mm. This record is thus not absolutely accurate, owing to inevitable observational error. It will be noted also in this connection

that the pressure in the constricting cuff was permitted to fall with considerable rapidity. The heart-rate in all of our subjects was approximately one per second, and the rate of fall of pressure was roughly 10 mm. in three seconds. Since the criteria of systolic and diastolic pressure are found in the altered character of the sphygmomanometer record, it is

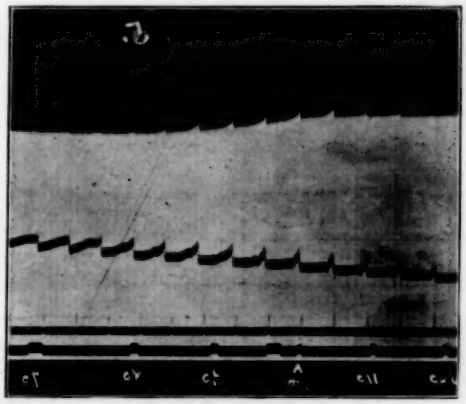

Fig. 3.—G. S. April 11, 1913. Narrow cuff.

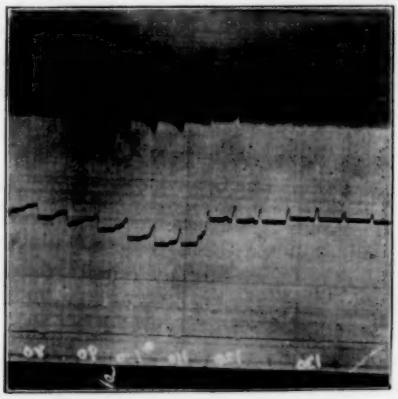

Fig. 4.—H. R. June 28, 1913. Narrow cuff.

obvious that the error of the method as depicted in the records here reproduced amounts to about 3 mm. of mercury. Although it would be desirable to avoid even this error, it is not a factor of great significance in blood-pressure work on man, nor in fact, in any observations in which pressure values are read in millimeters of mercury.

EXPERIMENTAL

With the instrumentation above described, sixteen records were obtained from four normal individuals. The figures from the records are presented in the accompanying table. It will be seen, as is evident in the records reproduced, that there is perfect agreement between the movements of the mercury capillary and of the Erlanger lever with respect to the points of both systolic and diastolic pressures.

TABLE OF VALUES FOR SYSTOLIC AND DIASTOLIC ARTERIAL BLOOD-PRESSURE AS RECORDED BY THE CAPILLARY ELECTROMETER AND THE ERLANGER SPHYGMOMANOMETER

Subject	Date	Cuff*	Arterial Blood-Pressure			
			By Capillary		By Erlanger	
			Systolic	Diastolic	Systolic	Diastolic
G. S.	5/11/13	†	115	75	115	75
G. S.	6/19/13	†	...	85	...	85
G. S.	6/19/13	‡	...	68	...	68
G. S.	6/25/13	‡	105	65	105	65
G. S.	6/25/13	†	135	95	135	95
M. U.	4/12/13	†	143	92	145	93
M. U.	6/30/13	‡	123	75	123	75
H. R.	6/20/13	‡	130	80	130	80
H. R.	6/20/13	†	140	95	140	95
H. R.	6/25/13	‡	120	75	120	77
H. R.	6/25/13	‡	115	85	115	85
H. R.	6/27/13	‡	115	83	115	83
H. R.	6/27/13	†	140	95	140	95
H. R.	6/28/13	‡	...	80	...	80
H. R.	6/28/13	†	130	90	130	90
C. D.	6/20/13	‡	117	85	118	85

* In this column † stands for narrow; ‡ for broad.

Two widths of cuff were used, 15 cm. and 5 cm. Although the actual pressure readings are materially higher with the narrow cuff, this factor did not disturb the agreement between the capillary and Erlanger values. It is proper to recall, however, that the broad cuff gives, as was shown by von Recklinghausen[4] and by Erlanger,[5] the more accurate figures; we made use of cuffs of different width in these observations simply to vary the experimental conditions of the test employed.

As to the causation of the brachial sound produced during observations of arterial blood-pressure we are inclined to adopt the explanation clearly set forth by Taussig and Cook, to wit, the systolic discharge of blood under the constricted area into a relatively empty section of vessel.

4. Von Recklinghausen: Arch. f. exper. Path. u. Pharmakol., 1901, xlvi, 86.
5. Erlanger: Johns Hopkins Hospital Report, 1904, xii, 105.

We had adopted a similar view, prior to publication by these authors, based on observation of the circulation schema, already mentioned. In such a system it is not only possible to hear the sounds under consideration, but at the same time to see the behavior of the vessel wall during their production. Under different conditions the sounds produced in such a system may take on the most varied tones, intensities and time relationships which suggests that the causative factors may be as complex as those controlling the shape of the ordinary pulse-wave. We did not pursue this phase of the subject for the reason that our schema gave a pulsatile wave of pressure widely divergent in form from the normal pulse-wave in animals and man, although it would seem to promise results of interest and perhaps of practical importance in clinical medicine. If, as maintained by the authors above quoted, the brachial sound may be heard in normal subjects at a point below diastolic pressure, an adequate explanation of the phenomenon ought to be forthcoming. Our results support the original interpretation of Korotkoff.

CONCLUSIONS

1. The method of Einthoven and Geluk for the graphic registration of sounds is described and applied to the brachial sound produced in arterial blood-pressure determinations.

2. The records show a very close agreement between the results of this method and the characteristic changes observed at systolic and diastolic pressure in synchronous tracings made with the Erlanger sphygmomanometer.

3. The conclusion is therefore reached that in normal subjects the onset of the brachial sound is coincident with systolic and the cessation of the sound is coincident with diastolic arterial blood-pressure.

A PATHOLOGICAL STUDY OF TWO CASES OF HEART-BLOCK WITH ADAMS-STOKES' SYNDROME *

EDWARD B. KRUMBHAAR, M.D.
PHILADELPHIA

In a recent very interesting report of a case of terminal heart-block, Pardee[1] demonstrates that an extensive anatomical lesion of the auriculoventricular bundle may be present without disturbance of its function. He then gives three lists: (1) ten cases, in which complete destruction of a transverse section of the bundle was invariably accompanied by complete heart-block; (2) six cases,[2] with varying degree of block, in which no lesion of the bundle existed; (3) ten cases, (six of complete and four of partial heart-block) accompanied by very slight pathological changes. The intermediate degrees of bundle involvement he has not considered. That is, though it has been firmly established that lesions of the conductive system may cause partial and complete heart-block, it seems also true that such lesions may exist (even though of considerable extent) without block; and further that partial or complete block may exist without lesion of the bundle.

The extracardiac origin of heart-block has long been suspected. Holberton[3] reported a case in which, after an injury to the neck, extreme bradycardia and "fainting fits" developed. At necropsy, adhesions pressing on the vagus were found with the heart normal. Again, Neuberger and Edinger[4] found, in a man suffering from chronic constipation, a marked bradycardia and fainting spells during defecation. The necropsy, by Weigert, disclosed a normal heart, but an infarction at the decussation of the pyramids with a small varix pressing on the nuclei and roots of the vagus. Recently it has been demonstrated[5] that stimulation of the left vagus can cause auriculoventricular dissociation.

---

*From the John Herr Musser Department of Research Medicine, University of Pennsylvania.

* Submitted for publication Nov. 18, 1913.

1. Pardee, H. E. B.: The Relation of Heart-Block to Lesions of the Auriculoventricular Bundle, with Report of a Case, THE ARCHIVES INT. MED., 1913, xi, 641.

2. One of these reported by me, Adams-Stokes' Syndrome with Complete Heart-Block, without Destruction of the Bundle of His (THE ARCHIVES INT. MED., 1910, v, 583), the first reported with complete block, Pardee incorrectly states to have followed typhoid. The exact cause was never ascertained, though it followed influenza, accompanied by a long period of physical and mental strain.

3. Holberton: Med.-Chir. Tr., London, 1841, Series 2, vi, 76.

4. Neuberger and Edinger: Berl. klin. Wchnschr., 1898, xxxv, 69.

5. Cohn, A. E.: Jour. Exp. Med., 1912, xv, 49.

Furthermore, it is generally conceded that ganglion cells and a rich plexus of nerve-fibers accompany the muscular system.[6] A complete pathological investigation should include, therefore, not only the sino-auricular node and the auriculoventricular system with its connections with the auricle and ventricle; but also the nerve-cells and fibers accompanying it, the vagi, and the central nervous system in neighborhood of the nuclei and roots of the vagi. This has not been done in the past for obvious reasons and will probably seldom be accomplished. It should also be remembered that even such an examination would fail to account for the functional type of block, caused by the action of toxins or deficient blood-supply.

For the purpose of determining the frequency of extensive lesions of the conductive system in the absence of heart-block, studies are now being conducted in this laboratory on appropriate post-mortem material.

In view of the increasing number of reports of heart-block, in which the clinical and pathological findings are contradictory, the following two cases are of interest, as in each case the findings at necropsy tally well with the clinical history. Unfortunately, in neither was it feasible to obtain polygraphic or electrocardiographic tracings during the period of block; but the clinical symptoms in each were of such a nature as to make it reasonably certain that at least transient block with Adams-Stokes' syndrome existed.

CASE 1.—Mrs. Kate H., aged 42, a housewife, was admitted to the Philadelphia General Hospital on the service of Dr. David Riesman Jan. 1, 1913, and died January 18.

Abstract of History.—For five weeks she had had cough with scanty and at times blood-tinged sputum. The cough had gradually been getting worse. There had been no definite loss of weight. On exertion there was dyspnea; but edema was not noted. She had to rise once at night to urinate. Her menses had ceased three months before. No noteworthy symptoms referable to the gastro-intestinal system were present.

She had no recollection of any previous illness, except an attack of rheumatism in 1903, which confined her to bed for seven weeks, and a "stroke" in May, 1911, which occurred with left-side paralysis during the night. The patient had been married ten years, had had no children, no miscarriages and no venereal history. She had used alcohol (principally beer) in moderation. A brother and a sister had died of nephritis.

Examination.—The skin was yellowish and transparent, mucous membranes very pale; nutrition fair. The arteries were hard and tortuous; pulse irregular, ranging from 70 to 80 at first, although occasionally it was 25 or 40. There was a tic of the facial muscles and tongue, more marked when talking. Severe pyorrhea alveolaris and follicular deposits in the tonsils were present. At the apex of the right lung were slight dulness and harsh breath-sounds. Posteriorly both lungs were resonant, but generalized bubbling râles were heard. The cardiac apex was palpable in the sixth interspace just inside the anterior axillary line. Dulness began above at the second rib, extended on the left to the apex and on the

6. Wilson: Proc. Royal Soc., 1909, lxxxi, Series B, 141.

right 1 cm. to the right of the right border of the sternum. On auscultation a loud, rough systolic murmur was heard at the pulmonary area, with reduplication and accentuation of the second sound; also a soft systolic murmur at the apex, not heard in the axilla or back. The abdomen was tympanitic. Tenderness could not be elicited and no organs or masses could be felt. The urine was reported negative, specific gravity 1.012.

Course.—January 8 the patient had a fainting spell. The patient next to her did not notice any convulsive movements. The pulse at 4:30 and 7 p. m. was 34. There were no visible pulsations in the neck.

Fig. 1—Case 1, heart 31; cellular infiltration of main bundle (more marked around small blood-vessel). Zeiss DD, eye-piece 4.

January 16 the resident physician observed the patient in an epileptiform attack. The breathing was stertorous, the head was drawn to the left and the left arm twitched momentarily. The pulse dropped from 60 to 24, the patient was mentally confused and poorly oriented. The following day several attacks occurred, one of which was observed by Dr. Farr. Both arms moved slightly and the eyes turned upward. There was a brief period of unconsciousness and after-

ward the patient complained that everything looked black. Dr. John H. Musser, Jr., took a polygraphic tracing on this date after an attack, but found no evidence of heart-block. The pulse was then 60. The following day the patient died.

Clinical Diagnosis.—Chronic myocarditis, mitral insufficiency, Adams-Stokes' syndrome, pulmonary edema, old hemiplegia (embolic).

Anatomical Diagnosis.—In addition to the preceding, mitral stenosis, sclerotic and infarcted kidneys.

Gross and Microscopic Examination.—Heart 31, hardened in formaldehyd. Weight 390 gm. Moderate amount of fat in epicardium. Coronary vessels slightly sclerosed. Left ventricle 10 to 14 mm. thick, cuts with increased resistance and numerous fibrous threads can be seen running through the musculature. On the septal surface the endocardium is diffusely thickened and opaque, as if by extension from the thickened mitral valve, but especially over the ramifications of the left branch of His' bundle. Similarly in the right ventricle there is fibrous thickening at the bases of the chordae tendinae in the septum. The surface of the septum shows a dense mass of fibrous tissue in its middle, and near the insertion of the mitral valve a cartilaginous, almost calcified mass. The aortic valves are distinctly thickened, irregular and calcified. Small patches of sclerosis are seen on the intima of the aorta. The mitral valve is in the form of a distinct "buttonhole," the opening being about 5 by 15 mm. The pulmonary and auriculoventricular valves are normal.

HISTOLOGICAL STUDY OF HIS' BUNDLE AND KEITH'S NODE

A section 3 cm. long and 3 cm. wide was cut from the septum to include Tawara's node, His' bundle and its bifurcation. The anterior and posterior borders of the piece are almost parallel with the long axis of the right ventricle, the inferior being slightly more anterior. Considering the heart as being upright in the body, oblique (almost sagittal) serial sections were cut from behind, forward and up. About one thousand were cut, of which five hundred were mounted and about one hundred and fifty stained. Every fourth slide was stained with hematoxylin and eosin, and the succeeding slide with Mallory's anilin-blue. In all the sections both auricle and ventricle appear, with the delicate auriculoventricular valve on the right side, and the thick stumps of the aortic and mitral valves on the left.

In the earlier sections (that is, posterior) the network of Tawara's node is well shown, lying close to the fibrous base of the mitral valve. Herein are considerable delicate fibrous connective-tissue and occasionally small collections of fat-cells, but this picture shows nothing definitely abnormal. The cellular infiltrate, however (small round cells and plasma cells), is distinctly more than is ever seen in normal tissue. As far as can be ascertained, after the fixation in formaldehyd, the muscle-fibers of the node, their connection with the auricular musculature and the auricular musculature itself are normal, with characteristic narrow fibers, faint cross striations, numerous nuclei and loose connective tissue in normal amounts.

In its course through the auriculoventricular groove, the structure of the bundle cannot be well studied, but the cellular infiltrate is still noticeable.

Lower down, where the main bundle sits on the ridge of the ventricular septum (owing to the plane of the section the bifurcation appears in the same sections), the fat and cellular infiltration is well shown. The right branch can be followed for a short distance imbedded in the ventricular musculature and then disappears, enveloped on three sides by a dense mass of scar tissue (Fig. 2). The sections above and below this show that it is a real obliteration. The left lies superficially beneath the endocardium and also shows the increased number of cells.

Histological Diagnosis.—Chronic interstitial myocarditis and valvulitis (aortic and mitral), cellular and fatty infiltration and fibrosis of His' bundle.

CASE 2.—Mrs. Hattie R., aged 41, a housewife, was admitted to the Presbyterian Hospital on the service of Dr. R. Pemberton, March 3, 1913, complaining of dyspnea.

History.—The usual symptoms of a chronic, severe heart-trouble were present; namely, dyspnea, edema of the legs and abdomen and occasional palpitation and

Fig. 2.—Case 1, heart 31; right branch, obliterated by fibrous tissue. Zeiss A, eye-piece 4. Two vertical bands of fibrous tissue (more dense and homogeneous than the surrounding myocardium) enclose the right branch of His' bundle. Near the center of the figure some cellular infiltrate appears in the muscle bundle, and just above this the two bands of fibrous tissue meet to obliterate it.

precordial pain, so severe that she could hardly walk. For three months she had had a severe cough. Four years before admission she had a febrile attack of rheumatism, sufficiently severe to confine her to bed for some days. Except for the usual diseases of childhood, her history and that of her family were negative.

Examination.—On admission her temperature was 99, pulse 108, respiration 38. Cardiac dulness extended from 1 cm. beyond the right border of the sternum to 2 cm. to the left of the midclavicular line. A presystolic murmur was noted with an accentuated second pulmonic sound. There was movable dulness in the abdomen and edema of the legs. Examination of eye fundi showed hemorrhagic retinitis. The urine contained a cloud of albumin and numerous hyalin casts. The Wassermann reaction was negative.

Course.—After three weeks of aggravation, and then of amelioration of the cardiac symptoms, fever set in with a leukocytosis of 26,000, and pelvic inflammation was diagnosed. On the day of her death, four typical Adams-Stokes' attacks were observed by Dr. Pemberton. With the pulse at 48, a violent epileptiform convulsion occurred, with loss of consciousness, jerking of limbs, bulging eyes, protruding tongue and stertorous breathing, and lasted perhaps three minutes. The pulse dropped to 14, but returned to the former rate after the attack. After recovering sufficiently to ask questions, she suffered another similar attack in which the pulse dropped to 24. In the third attack it was noted that the heart stopped entirely for some seconds; in the fourth and fatal attack, respirations stopped two minutes after the cessation of the heart-beat. No opportunity was offered for graphic registration of heart-beat and pulse. Necropsy was performed by Dr. C. B. Farr four hours after death.

Anatomical Diagnosis.—Double pyosalpinx, acute seropurulent peritonitis, acute fibrinous pericarditis and pleuritis with right-sided effusion; hypertrophy and dilatation of heart; mitral stenosis; atheroma of aorta; chronic diffuse nephritis; chronic passive congestion of liver and spleen; parenchymatous degeneration of liver.

Gross and Microscopic Examination.—Heart 15, received in formaldehyd, weight 650 gm. Parietal and visceral pericardium much thickened with heavy deposits of fibrin, obscuring the various relations of heart. Pneumogastric terminations could not be found. Heart is homogeneous, yellowish-brown, firm, and cuts with increased resistance; fibrous strands are visible here and there, and several grayish, translucent nodules are seen. The left ventricle is from 12 to 14 mm. thick; the right ventricle from 4 to 6 mm. The trabeculae are well developed. The aortic valves are distinctly thickened with numerous atheromatous patches on the ascending arch of the aorta. The mitral valve is much stenosed and thickened but without distinct nodules. The left ventricular branch of His' bundle is visible as a fan-shaped, spreading bundle. One so-called abnormal tendon fiber with very slight endocardial thickening runs to the posterior papillary muscle. No other abnormality is visible. The coronary arteries are diffusely sclerosed.

HISTOLOGICAL DESCRIPTION

The whole heart septum from the lower border of the fossa ovalis in the auricle to the apex of the ventricle was removed and cut into blocks suitable for serial section. The anterior and posterior borders were cut almost parallel to the long axis of the right ventricle with the lower portion slightly forward and the superior and inferior at right angles. One piece of tissue was cut to include Tawara's node and as much as possible of His' bundle, and sections were taken on the frontal plane. In spite of fixation in formaldehyd excellent histological detail was as a rule shown.

In the earlier sections, the muscular network of Tawara's node was found normal. Adjacent to it, beneath the endocardium of the right ventricle, were numerous swollen, vacuolated, faintly striated cells resembling Purkinje fibers. Some of these contained hemosiderin pigment granules. A small collection of plasma and small round cells were present on the edge of Tawara's node.

In later sections these small collections were found to contain many polymorphonuclear leukocytes (10 to 40 per cent). They occur both subendocardial and buried deep in fibrous or muscular tissue, usually around small vessels.

In later sections, in which the bundle was found traversing the fibrous band between the auricle and ventricle, it was approximately normal with little or no increase of fibrous tissue. The same deposits of small round cells, plasmacells and leukocytes were found in it.

Still later the division of the bundle was shown, but the right branch could not be followed well owing to poor fixation. The left appeared in cross-section or oblique section immediately beneath the endocardium. The musculature in its upper portion, was about normal, though it also was poorly fixed. Further down, the chains of Purkinje-like cells, well separated by loose fibrous tissue from each other and from the ventricular musculature, were well shown. The cellular foci before described were also present and were much more abundant than through the ventricular muscle proper. These foci could be followed the length of the septum, with occasional extensions into the septa between the ventricular muscle bundles. The actual junction of the Purkinje fibers with the muscle-fibers was not seen. The base of the auriculoventricular valve appeared edematous and contained similar cellular foci. The valve showed no acute endocarditis. A diffuse fibrosis of considerable extent existed throughout the ventricular musculature. In places, dense fibrous masses without nuclei were found at times with a core of more fibrous tissue, and one of these occurred subendocardially directly in the path of the left branch (gumma).

Sections from Keith's node (parallel to the crista terminalis, 8 by 20 mm.) failed to reveal any abnormality, other than the inclusion of a small number of cells similar to those described above.

Histological Diagnosis.—Acute inflammation of Tawara's node and bundle of His; diffuse fibrosis and multiple gummata of ventricle.

SUMMARY

In Case 1, in which there were transient attacks of heart-block, complicated with Adams-Stokes' syndrome during the last eight days of life, there was found a marked cellular infiltration of the auriculoventricular conductive system. Furthermore, the right branch was found completely obliterated, showing that total destruction of one branch is compatible with an at times normal pulse.

In Case 2, chronic salpingitis, in a woman who sought the hospital for relief from a chronic rheumatic endocarditis with failing compensation, the hitherto localized septic process caused, three weeks after admission, a general peritonitis, pleuritis, pericarditis, and localized areas of acute myocarditis, especially in His' bundle and Tawara's node. On the day of her death, due presumably to the heart-block thus caused, there occurred four typical attacks of Adams-Stokes' syndrome, the last of which was fatal. The only other reported case that I know of in which an acute septic condition of the conducting system was associated with heart-block is that reported by Gerhardt,[7] in which a patient who had

7. Gerhardt: Deutsch. Arch. f. klin. Med., 1908, xcii, 485.

just recovered from an attack of acute articular rheumatism with temporary heart-block succumbed to typhoid fever, and at necropsy a perivascular cellular infiltration was found in His' bundle, the residuum of an acute inflammation.

I am indebted to Drs. Riesman, Farr and Pemberton for the clinical reports and necropsy material.

THE COAGULATION OF NORMAL HUMAN BLOOD

AN EXPERIMENTAL STUDY *

ROGER I. LEE, M.D., AND BETH VINCENT, M.D.
BOSTON, MASS.

INTRODUCTION

This paper represents a study of the essential processes involved in the coagulation of blood along lines recently worked out by Bordet and Delange.[1]

This work has been carried out entirely with human blood. Nearly all the investigators in the field of coagulation of blood have worked with the blood of the lower animals. Bordet and Delange worked mostly with rabbits, somewhat with guinea-pigs and not at all with human blood. We have attempted to parallel the experiments of Bordet and Delange on rabbit's blood with experiments on human blood. We felt that such a study would not only confirm the important conclusions of Bordet and Delange but might perhaps permit a basis for deductions of clinical value. In addition we have subjected to critical study the procedures and experiments of Bordet and Delange and have attempted to carry still further the investigation of the problem of coagulation.

The literature on coagulation of blood is voluminous. Morawitz[2] in an excellent summary of the subject in 1905 gives a bibliography of 490 articles. There are many conflicting theories. The theory of Morawitz,[2,3] which is essentially identical with that of Fuld,[4,5] and the theory of Howell,[6] are perhaps the best known. Nolf,[7] Loeb[8] and DeWaele[9] are among the many who have advanced theories which differ to a greater or less extent from those of Morawitz and Howell. The whole subject has

---

* From the Pathological Laboratory of the Massachusetts General Hospital.
* Submitted for publication Sept. 20, 1913.

1. Bordet, J., and Delange, L.: Ann. de l'Inst. Pasteur, 1912, xxvi, 657. 737.
2. Morawitz, P.: Ergebn. d. Physiol., 1905, iv, 307, Parts 1 and 2.
2. Morawitz, P.: Ergebn. de Physiol., iv, Jahr. Abt. 1 and 2, 1905, p. 307.
3. Morawitz, P.: Beitr. z. chem. Phys. u. Path. (Hofmeister's), 1903, iv, 381; Deutsch. Arch. f. klin. med., 1904, lxxix, 1, 215; Handbuch der Biochemischen Arbeitsmethoden, E. Abderhalden, 1911, v, 223.
4. Fuld, E.: Zentralbl. f. Physiol., 1903, xvii, 529.
5. Fuld, E., and Spiro, K.: Beitr. z. chem. Phys. u. Path. (Hofmeister's), 1904, v, 171.
6. Howell, W. H.: Am. Jour. Physiol., 1910, xxvi, 453; 1911, xxix, 187; 1912, xxxi, 1.
7. Nolf, P.: Arch. Internat. de Physiol., 1908, vi, 1, 115.
8. Loeb, L.: Beitr. z. chem. Phys. u. Path. (Hofmeister's), 1905, vi, 260.
9. De Waele, H.: Ztschr. f. Immunitätsforsch., 1912, xvi, 311.

been considerably complicated by the large number of terms used by the various workers. In some instances the same term is used to denote quite dissimilar substances. In other instances different workers have attributed to apparently the same substance quite divergent characteristics. The problem has been attacked from so many points of view that it is often impossible to parallel the fundamental principles of the various theories. In this paper no attempt will be made to discuss in detail the various theories.

Bordet and Delange have approached the problem of coagulation from a somewhat different angle from most of the previous work. They have used a different terminology from Morawitz, Fuld or Howell. The theory of Bordet and Delange may be simply stated as follows:

The coagulation of normal blood consists essentially of three steps:

1. Blood on being shed immediately undergoes some change which makes it quite different from the normal circulating blood and enables coagulation to ensue. Concerning this important initial step very little is known. The duration of this stage is unknown, it is probably very short. This is in agreement with practically all the theories on the subject of coagulation.

2. The second step is the formation of thrombin or the active coagulating principle of the blood. The duration of this stage can be measured and is probably the varying factor in the length of time required for coagulation. According to the theory of Bordet and Delange thrombin is formed by the reaction between cytozyme and serozyme in the presence of a soluble calcium salt.

Cytozyme in the blood is chiefly derived from the platelets, to a much less extent from the white corpuscles. Outside of the blood this active principle is found in the tissue juices. The cytozyme of Bordet and Delange is roughly comparable to Howell's thromboplastic substance and Morawitz' thrombokinase. Serozyme is a substance contained in blood-serum which unites with the cytozyme to form thrombin. Serozyme is not present as such in the circulating blood or in the oxalated plasma. Serozyme may be considered as comparable to the prothrombin of Howell and the thrombogen of Morawitz. While all workers in this field agree that thrombin is the coagulating substance which is produced in the blood, there are radical differences as to the method of the formation of thrombin and the substances used in its production.

3. The third stage is the action of the thrombin when formed on the fibrinogen of the blood changing the fibrinogen into fibrin and causing coagulation. Calcium is not required for this stage. The duration of this stage under favorable conditions is probably within two minutes. Here again practically all of the workers are agreed on the general principle of this step.

Bordet and Delange admit the possibility of the presence and the action in the first stage of an antithrombin, which plays an important rôle in the theory of Howell and the presence of which is conceded by most observers. In Howell's theory antithrombin is the substance that keeps blood fluid in the vessels and it is only by the neutralization, as it were, of antithrombin by the thromboplastic substance (the cytozyme of Bordet and Delange), that prothrombin is set free and permitted to be changed to thrombin.

COLLECTION AND PREPARATION OF THE BLOOD

In collecting and preparing the blood from human beings for these experiments, the method prescribed by Bordet and Delange based on the original technic of Mosen[10] for animals was followed with slight modification. As pointed out by those writers, it was found that the experimental results were not consistent or accurate unless the blood had been obtained under conditions which prevented the occurrence of any part of the process of coagulation during this procedure. For this reason the technic of collecting the blood will be described in detail.

The essential point in this technic is to oxalate the blood. This precipitates the calcium. By this process of decalcification the blood is rendered spontaneously incoagulable before any of the preliminary steps of coagulation have taken place. This was accomplished by taking the blood directly from the veins through a glass tube, coated with paraffin, into a paraffined flask containing a solution of sodium oxalate. Preliminary to securing the blood a small glass tube about 5 cm. long and 4 mm. in diameter and four Erlenmeyer flasks holding 150 c.c. were sterilized, dried and coated with paraffin.[11] The flasks were graduated to 100 c.c. and in each flask was placed 10 c.c. of 1 per cent. sodium oxalate solution in salt solution 0.5 to 100. The blood for these experiments was obtained from patients in the medical wards of the Massachusetts General Hospital. All the patients had essentially normal blood. The hemoglobin, cell counts and platelet counts were within normal limits. The coagulation times by the method described by Lee and White[12] were also within normal limits.

The slight operation necessary to collect the blood was done with the ordinary aseptic precautions. The arm of the patient, having been surgically prepared, is placed at right angles to the bed with the forearm resting on a small table and the median bacillic vein is exposed for about one inch under local anesthesia. The vessel is tied above and temporarily

10. Mosen, R.: Arch. f. Anat. u. Physiol., Physiol. Abt., 1893, p. 352.

11. The paraffin used in these experiments was obtained from the Bausch & Lomb Optical Company, Rochester, N. Y., and labeled "Best white imported paraffin, melting-point 45 to 50 C." (122 F.)

12. Lee, R. I., and White, P. D.: Am. Jour. Med. Sec., 1913, cxlv, 495.

occluded below with a light artery clip or by making traction upward on a silk thread passed under the vessel. The glass tube is then inserted into the vein and secured with a ligature. Previous to this step a tourniquet is applied above the elbow, tight enough to obstruct the venous return. When the clamp is removed from the vein, the blood flows from the end of the tube with considerable pressure. After wasting the first few cubic centimeters, the blood is allowed to fall directly into the oxalate solution in the paraffined flasks until the level of the mixture reaches the 100 c.c. mark. This gives a spontaneously incoagulable blood, oxalated 1 to 1,000. With the exception of the paraffin coating of the tube and flask the blood has not been in contact with a foreign body until decalcified by the sodium oxalate solution. This oxalated blood is immediately subjected to fractional centrifugalization to separate the plasma and the cellular elements. The blood is first poured into several centrifugal tubes and whirled at a moderate rate of speed for about fifteen minutes which gives a precipitate and a supernatant fluid. The precipitate consists of a small white deposit of calcium oxalate at the bottom of the tube and a broad layer of red cells surmounted by a thin "buffy coat" of white corpuscles. Some platelets are also carried down with the red and the white cells. The supernatant fluid, which is then drawn off with a pipet, is a yellowish plasma, clouded by the platelets which for the most part have remained in suspension after moderate centrifugalization. Microscopic examination of a drop of this fluid shows that in addition to platelets, it still contains a few red and white cells. If the supernatant fluid is centrifugalized at a higher rate of speed for fifteen minutes, the red and white corpuscles which remain can be precipitated with some blood-platelets, leaving a plasma containing no cells except the platelets. This fluid, rich in platelets, is called "cloudy plasma" and will be frequently referred to as such in the subsequent experiments. The cloudy plasma is then given a second, more prolonged and rapid centrifugalization, usually about an hour with four thousand revolutions to the minute, which throws down the platelets in a tenacious clump in the bottom of the tube leaving a supernatant fluid of clear amber plasma. This is termed the "clear plasma." It still contains a few platelets which can be largely eliminated by repeating the centrifugalization for another hour. The resulting supernatant fluid which looks like the clear plasma but does not contain so many platelets is termed "very clear plasma." The number of platelets in the plasma depends on the energy of centrifugalization. The cloudy plasma has many, the clear plasma less and the very clear plasma only a few. Theoretically, it might seem possible so to prolong the centrifugalization as to free the plasma entirely of platelets. We have never been able to obtain such a plasma and this corresponds with the experience of Bordet and Delange. After

a thorough washing in physiological salt solution containing 0.5:1,000 sodium oxalate, the platelets are made into a thick suspension in the same fluid. Some difficulty is experienced in breaking up the clump of sticky platelets. This can be most easily done by repeatedly drawing the platelets up into a small pipet and forcing them out through the fine point of the pipet, which rests against the bottom of a tube. After each washing the platelets are thrown down by rapid centrifugalization. Usually two or three washings are sufficient. The yield of platelets varies with the individual blood and the care with which the blood has been collected and put through the process of centrifugalization. From 200 c.c. of oxalated blood a thick suspension of platelets can usually be obtained which on standing gives a sediment of platelets about 2 cm. in depth in a tube of 7 mm. diameter. The plasma solutions obtained by this procedure, if kept in the cold, remain unaltered and suitable for experimental purposes for from four to six days. If some error has been made in the preparation a light cloud appears in the liquid. The suspension of platelets is more stable if kept in the cold and if sterilized, as described later in the paper, can be used for several months.

In the course of our work an effort was made to simplify the technic of collecting the blood (exposure of a vein and the use of a coated glass tube) by resorting to the usual clinical method of puncturing the vein at the elbow through the skin and drawing the blood through a needle into a paraffined vessel containing oxalate solution. This was tried on several patients and no difficulty was experienced in obtaining the blood but such blood did not give so good a yield of platelets or furnish plasma so clear or stable as was obtainable from blood taken by the other method. Even a brief contact with such foreign bodies as the metal needle and the rubber tube before the blood has been oxalated appeared to be sufficient to precipitate some of the earlier stages of coagulation. Although these reactions may not have progressed so far as actual fibrin formation, the blood is so altered that certain of the more delicate experiments can not be performed. We came to the conclusion that for experimental purposes at least it is necessary to obtain the blood by the somewhat laborious method which has been described.

In addition to cloudy plasma, clear plasma, very clear plasma and the suspension of platelets, three chemical solutions are prepared for use in the subsequent experiments.

Decalcifying Oxalate Solution, 1:100.—This is made by adding sodium oxalate in the proportion of one part to one hundred of a 0.5 per cent. salt solution. This is the stock solution which is used whenever it is necessary to oxalate the blood.

Physiological Oxalate Solution.—This solution, which is used in washing and making up the suspension of platelets, consists of physiological salt solution (0.9 per cent.) oxalated to 0.5 parts in 1,000.

Recalcifying Fluid.—This solution is made by adding 770 c.c. of salt solution to 30 c.c. of a 1:100 calcium-chlorid solution. The exact strength of this 1 per cent. calcium-chlorid solution is such that one volume will completely precipitate an equal volume of 1:100 oxalate solution. Four volumes of the recalcifying solution contains one and one-half the calcium needed to neutralize the oxalate in one volume of the plasma solution, oxalated 1 to 1,000.

Fibrinogen.—The clear oxalated plasma is used by Bordet and Delange as a solution of fibrinogen to test the coagulating power of any given solution. For this purpose they prefer the oxalated plasma to the pure fibrinogen solutions (which are made by repeatedly precipitating the fibrinogen with concentrated sodium-chlorid solutions) because it is so difficult to obtain by this method fibrinogen which is not contaminated by a trace of some one of the coagulating agents. The oxalated plasma contains in addition to fibrinogen, some elements from which cytozyme and serozyme are derived; but as will be explained later these agents are rendered inert by the excess of oxalate.

This test solution is frequently used by Bordet and Delange in the form of a diluted "monoxalated plasma" and a diluted "dioxalated plasma." The diluted "monoxalated plasma" is made by diluting the clear oxalated plasma with four volumes of a 1 to 1,000 oxalate solution. This 1:1,000 oxalate solution is made by adding one volume of a 1:100 oxalate solution to nine volumes of normal salt solution. The diluted "dioxalated plasma" is made by diluting the clear oxalated plasma with four volumes of a 2:1,000 oxalate solution which consists of eight parts of normal salt solution and two parts of a 1:100 oxalate solution.

Cytozyme.—The platelets which are obtained in the process of fractional centrifugalization are the chief source of cytozyme. This element is also found in the white corpuscles and tissue juices; but in the experiments which follow, the washed suspension of platelets is usually employed when a cytozymic action is desired.

Serozyme.—As will be demonstrated later, serozyme is found in the serum which is obtained by defibrinating the coagulated clear plasma. When freshly made this serum also contains some active thrombin. The thrombin is rapidly enfeebled by age and has almost disappeared in serum which is 24 hours old. This 24-hour old serum is used by Bordet and Delange as the serozyme solution. "Salted plasma": In addition to sodium oxalate other salts such as sodium chlorid and sodium citrate are employed to make an incoagulable plasma. Blood obtained as described above is "salted" by collecting it in a flask containing a 20 per cent. sodium-chlorid solution in such an amount that the final plasma contains 5 per cent. sodium chlorid. The red and white corpuscles are removed by centrifugalization, leaving a clear red plasma. This so-called salted

plasma is spontaneously incoagulable although it contains calcium. If the proper proportion of sodium chlorid is reestablished by the addition of distilled water (four volumes) coagulation will take place in this plasma.

Our experimental studies have dealt especially with three factors in coagulation: cytozyme, serozyme and thrombin. The other two important factors in coagulation, calcium and fibrinogen, will be discussed only incidentally, since all observers are in essential agreement as to the part which they play in coagulation. The purpose of this study is to investigate the nature and action of the three substances denominated by Bordet and Delange, cytozyme, serozyme and thrombin.

In our work we have retained the terms used by Bordet and Delange. The words "cytozyme" and "serozyme" imply from their derivation the characteristics of an enzyme. We shall show later that cytozyme and serozyme do not act like enzymes.

CYTOZYME

The cytozyme of Bordet and Delange corresponds fairly closely to the thrombokinase of Morawitz and the thromboplastic substance of Howell.

According to Bordet and Delange the active principle, cytozyme, is contained in the blood-platelets, in tissue juice, and to a much less extent in the white corpuscles of the blood.

BLOOD PLATELETS AS A SOURCE OF CYTOZYME

The importance of blood-platelets in coagulation, which has been recognized since the work of Bizzozero[13] and Hayem[14] about 1880, can be demonstrated in various ways. Cloudy oxalated plasma, which is the oxalated blood centrifugalized for about fifteen minutes at low speed, will clot in from eight to fifteen minutes after the addition of recalcifying fluid. By further centrifugalization for one hour, one obtains what we call clear plasma; very clear plasma is obtained by centrifugalization for two hours. The only difference in these plasmas is their content of blood-platelets. Examination of the sediment of the centrifugalized plasma after the removal of the red blood-corpuscles shows only blood-platelets and a rare leukocyte. The average coagulation time of clear plasma is from twenty-five to thirty-five minutes. At times we have succeeded in obtaining a very clear plasma which requires forty-five minutes to coagulate on being recalcified. If blood-platelets are added, either from the same blood or from another blood, one obtains again cloudy plasma which will clot in the time of the original cloudy plasma, which is from eight to fifteen minutes. In short, the coagulation time of the recalcified oxalated

13. Bizzozero, J.: Virchows Arch. f. Path. Anat. u. Phys., 1882, lxl, 261.
14. Hayem, G.: Du sang et de ses altérations anatomiques, Paris, 1889, p. 291.

plasma depends on the number of blood-platelets in the plasma. This phenomenon was first demonstrated by Mosen[10] in 1893. An illustrative protocol follows:

Experiment 1.—Take four tubes, A, B, C and D; in A is 1 c.c. of oxalated cloudy plasma and 6 drops of the suspension of platelets. In B is 1 c.c. of oxalated cloudy plasma. In C is 1 c.c. of oxalated clear plasma (cloudy plasma centrifugalized one hour). In D is oxalated very clear plasma (cloudy plasma centrifugalized two hours). To each tube add 4 c.c. of the recalcifying fluid. A clots in five minutes, B in ten minutes, C in twenty-five minutes and D in forty minutes.

We have never been able to obtain a plasma which was incoagulable on recalcification by centrifugalization, no matter how prolonged. This coincides with the experience of Bordet and Delange.

If to the clear oxalated plasma, however, nine volumes of distilled water is added and a current of carbon dioxid is passed through, a turbidity appears. The plasma is then centrifugalized and clear fluid is obtained which either does not clot or clots very slowly on being recalcified and by replacing the sodium chlorid. This clear fluid will clot, however, on the addition of blood-platelets. Bordet and Delange assume that the carbon dioxid with the distilled water causes a precipitation of some substances which allows the blood-platelets to be more easily removed by centrifugalization.

Experiment 2.—To 1 c.c. of clear oxalated plasma add 9 volumes of distilled water. Pass a current of carbon dioxid through the mixture, a turbidity appears, centrifugalize energetically. Pour into Tube A 5 c.c. of the clear supernatant fluid. Into Tube B the remaining 5 c.c. after shaking. Then replace the sodium chlorid and add calcium by adding 0.2 c.c. of a 20 per cent. solution of sodium chlorid and 0.2 c.c. of a 0.5 per cent. of calcium chlorid to each tube. B clots firmly in twenty-five minutes; A shows only a moderate clot the next day.

THE SOLUBLE ACTIVE PRINCIPLE OF PLATELETS

The presence of the blood-platelets themselves is not essential to coagulation. Strong saline solutions apparently have the power of dissolving the active principle of the platelets.

Experiment 3.—If the blood is taken into a solution of sodium chlorid instead of sodium oxalate (40 c.c. of blood and 10 c.c. of 20 per cent. sodium chlorid) this plasma, the so-called "salted" plasma, is spontaneously incoagulable. But no matter how energetic or how prolonged is the centrifugalization of this plasma it clots in three to five minutes on the addition of four volumes of distilled water with 0.015 per cent. calcium chlorid.

The plasma can be microscopically demonstrated to be practically free from platelets. Therefore the actual presence of blood-platelets is not necessary for coagulation.

Bordet and Delange have shown that by heating a solution of blood-platelets in salt solution and keeping the solution for some time, they can obtain a clear supernatant fluid without blood-platelets yet causing coagu-

lation. Howell,[6] Austin and Pepper[14] and others have shown that the active coagulating principle in the blood-platelets while essentially insoluble in normal salt solution is soluble in distilled water. We have left distilled water in contact with blood-platelets for two hours and then found that the fluid freed from the blood-platelets by centrifugalization has essentially the same effect as the blood-platelets themselves.

Experiment 4.—Five tubes, A, B, C, D and E. In each tube put 0.4 c.c. of the recalcifying fluid and 0.1 c.c. of serum (obtained the day before by defibrination of the clot formed by the mixture of 1 c.c. of clear oxalated plasma and 4 c.c. of the recalcifying fluid). To A add nothing. To B add 1 drop of the suspension of platelets. To C add 1 drop of the supernatant fluid of the suspension of platelets, kept for two weeks after heating to 100 C. for fifteen minutes. To D add 1 drop of the supernatant fluid obtained by centrifugalization of a mixture of platelets and distilled water after two hours of contact. To E add 1 drop of clear supernatant fluid obtained by centrifugalization of the suspension of platelets in normal salt solution. After fifteen minutes add 0.5 c.c. of the diluted dioxalated plasma. B, C and D coagulate in two or three minutes; A and E do not coagulate even the next day.

It is evident, therefore, that the suspension of blood-platelets, the extract of platelets in sterile water, and the heated extract in salt solution are all equally effective. But without blood-platelets or some active extract of them, there is no coagulation.

Blood-platelets alone either in thick suspension or in a solution of distilled water (with or without calcium) do not cause the coagulation of fibrinogen.

Experiment 5.—Four tubes, A, B, C and D. In Tube A, 0.5 c.c. of suspension of platelets; in Tube B, 0.5. c.c. of the suspension of platelets and 0.5 c.c. of the recalcifying fluid. In Tube C, 0.5 c.c. of solution of the platelets is distilled water. In Tube D, 0.5 c.c. of the solution of platelets in distilled water and 0.5 c.c. of the recalcifying fluid. After fifteen minutes add 0.5 c.c. of the diluted dioxalated plasma to each tube. There is no coagulation in any of the tubes.

THE QUANTITATIVE ACTION OF PLATELETS

Various observers have maintained that the action of the blood-platelets is essentially that of an enzyme, i. e., that a small amount of the active principle of blood-platelets can be used repeatedly in assisting coagulation. This is shown not to be the case by the fact cited above, that the coagulation time of the recalcified oxalated plasma varies approximately with the number of blood-platelets in the plasma. An oxalated plasma, rich in blood-platelets, coagulates in five to ten minutes on recalcification. The oxalated plasma, poor in platelets, which coagulates in thirty minutes on recalcification, coagulates in five to ten minutes on the simple addition of platelets before recalcification.

---

15. Austin, J. Harold, and Pepper, O. H. P.: Experimental Observations on the Coagulation of Oxalated Plasma with a Study of Some Cases of Purpura, THE ARCHIVES INT., MED., 1913, xi, 305.

The accurate measuring of the platelets in the suspension is very difficult. It is possible, however, to use suspensions of different opacities and thus to secure suspensions of different strengths. It is possible to obtain a suspension so poor in platelets that no coagulation ensues when all the other elements are added in their usual quantities.

Experiment 6.—Two tubes, A and B. In each put 0.4 c.c. of the recalcifying fluid and 0.1 c.c. of serum. Add to A 1 drop of ordinary suspension of platelets; to B 1 drop of a very thin suspension of platelets. After fifteen minutes add 0.5 c.c. of diluted dioxalated plasma. Coagulation takes place in two minutes in A; there is no coagulation in B.

It has been shown, therefore, that the platelets act in a quantitative manner, and that there is a minimum amount of platelets required to furnish sufficient thrombin to coagulate a given amount of fibrinogen.

RESISTANCE TO HEAT; PRESERVATION OF BLOOD-PLATELETS

Suspensions of blood-platelets can be heated at 100 C. for fifteen minutes without interfering with their activity in assisting coagulation. We have even exposed suspension of blood-platelets to dry heat at 120 C. for fifteen minutes and find that the blood-platelets have not lost their activity. A sterile suspension of blood-platelets maintains its activity as a factor in coagulation apparently unimpaired for several weeks.

Experiment 7.—Four tubes, A, B, C and D. In each tube is placed 0.4 c.c. of the recalcifying fluid and 0.1 c.c. of serum. To Tube A add 1 drop of the suspension of platelets. To Tube B add 1 drop of the suspension of platelets, heated at 100 C. for fifteen minutes; to Tube C 1 drop of the suspension of platelets heated to 120 C. for fifteen minutes; to Tube D add 1 drop of the suspension of platelets kept in the refrigerator for several weeks after heating to 100 C. After fifteen minutes add to each tube 0.5 c.c. of diluted dioxalated plasma. A, B and D clot firmly in two to three minutes and C clots firmly in three to five minutes.

THE RÔLE OF PLATELETS IN CLOT RETRACTION

LeSourd and Pagniez[16] and others have pointed out that blood-platelets have a remarkable effect in causing a retraction of the clot. The following typical protocol is convincing:

Experiment 8.—If clear oxalated plasma is recalcified and the clot left for several days there will be only a slight retraction of the clot. However, if to 1 c.c. of the cloudy plasma is added 30 drops of a thick suspension of platelets and then 4 c.c. of recalcifying fluid is added, coagulation takes place in about six minutes and strong retraction begins in less than an hour. The clot is retracted down at the end of two days to the size of a small almond in the midst of clear fluid. If this clot is removed and microscopic sections are made and stained by Wright's[17] method of staining blood-platelets in tissues, one sees the following typical appearance: The clot appears like some homogeneous colloid material, no fibrin threads are seen; scattered through the clot are well-preserved platelets and here and there strands of material resembling fused conglomerate platelets. Clots formed with the use of a solution of platelets do not retract.

16. Le Sourd, L., and Pagniez, P.: Jour. de phys. et path. gen., 1907, ix, 579.
17. Wright, J. H.: Jour. Morphol., 1910, xxi, No. 2.

This relation of the blood-platelets to the retraction of the clot has been observed clinically by various writers besides Bordet and Delange, especially by Hayem[18] and Duke.[19] LeSourd and Pagniez[20] have recently used this property of blood-platelets as a biologic test for the presence of blood-platelets in various organs.

RED BLOOD-CORPUSCLES AS CYTOZYME

We have tried various substances to test their efficiency in replacing blood-platelets. Austin and Pepper[15] conclude from their experiments that all the corpuscular elements of the blood yielded the same active principle in assisting coagulation that is found in the blood-platelets. We feel that their technic is open to serious criticism, since our experience has shown, as we have said, that unless the most careful precautions are used blood-platelets are diffused through the whole blood. We have taken suspensions of red blood-corpuscles from the lower third of the resulting sediment obtained by the first centrifugalization of the oxalated blood. Such suspensions of red blood-corpuscles, thoroughly washed, are not effective in replacing the blood-platelets. We used very thick suspensions and as much as 10 to 15 drops of the suspension of red blood-corpuscles in contrast with 1 drop of the suspension of platelets yet no coagulation occurred. Furthermore, distilled water left in contact with the red blood-corpuscles does not show any activity in assisting coagulation.

Like the platelets, the suspensions of the red blood-corpuscles are not able of themselves to coagulate fibrinogen with or without the presence of calcium.

Experiment 9.—Five tubes, A, B, C, D and E. In A, B and C put 0.4 c.c. of the recalcifying fluid and 0.1 c.c. of serum; in D put 0.5 c.c. of the recalcifying fluid; in E, 0.5 c.c. of physiological salt solution; to A add 1 drop of the suspension of platelets; to B add several drops of the suspension of red blood-corpuscles; to C add several drops of the supernatant fluid of a mixture of distilled water and red blood-corpuscles which has been in contact for over two hours. To D and E add several drops of the suspension of red blood-corpuscles. After fifteen minutes add 0.5 c.c. of diluted dioxalated plasma. Coagulation in three minutes in A, no coagulation in B, C, D or E.

We are therefore forced to conclude that the red blood-corpuscles do not possess any activity as cytozyme.

WHITE CORPUSCLES AS CYTOZYME

Bordet and Delange injected sterile bouillon into the peritoneal cavity of guinea-pigs and obtained a fluid rich in leukocytes but containing no other cellular elements of the blood. This fluid clotted very slowly

18. Hayem, G.: Leçons sur les maladies du sang, Paris, 1900, p. 77.

19. Duke, W. W.: The Pathogenesis of Purpura Hemorrhagica with Especial Reference to the Part Played by Blood-Platelets, THE ARCHIVES INT. MED., 1912, x, 445.

20. Le Sourd, L., and Pagniez, P.: Compt. rend. de sc. Par., 1913, lxxiv, 580.

spontaneously. The addition of platelets to this fluid caused a more rapid coagulation. Bordet and Delange conclude from this experiment that leukocytes furnished some cytozyme, but to a much less degree than platelets. As we worked with human material so far as possible, we did not repeat this experiment. We are not able to obtain leukocytes from the blood without the presence of large numbers of blood-platelets. We obtained leukocytes from various sources, however. We obtained leukocytes in three cases of pleural empyema, in two cases due to the pneumococcus, and one case to the streptococcus pyogenes. We also obtained leukocytes from the urinary sediment of a case of cystitis and also from the meningeal exudate in a case of epidemic cerebrospinal meningitis.

Microscopical examination of this material showed in every case no formed elements except the leukocytes. The material was washed many times with normal salt solution, containing a trace of sodium oxalate, and finally suspensions of the leukocytes were made in this fluid. These suspensions corresponded in opacity to the suspension of blood-platelets. Contrary to the findings of Bordet and Delange, we were unable in parallel experiments, repeated many times, to detect any constant real difference between the activity of the platelet suspensions and that of the leukocyte suspensions. Further, the suspension of leukocytes resisted heat in a manner precisely similar to the blood-platelets. Moreover if distilled water is left in contact with leukocytes and the leukocytes are then removed by centrifugalization, we get a solution which is active in assisting coagulation. But the clots formed by the use of this suspension of leukocytes did not retract.

Experiment 10.—Five tubes, A, B, C, D and E. To each tube is added 0.4 c.c. of the recalcifying fluid and 0.1 c.c. of serum. To Tube A add 1 drop of the suspension of platelets; to tube B 1 drop of the suspension of leukocytes is added; to Tube C 1 drop of the suspension of leukocytes heated to 100 C. for fifteen minutes. To Tube D 1 drop of the clear supernatant fluid of the mixture of leukocytes with salt solution. To Tube E 1 drop of the clear supernatant fluid of the mixture of leukocytes and distilled water after contact for two hours. After fifteen minutes add 0.5 c.c. of diluted dioxalated plasma to each tube. Coagulation takes place in from two to three minutes in A, B, C and E, but does not take place in Tube D.

The leukocyte suspension seems as effective as the blood-platelet suspension in assisting coagulation.

We are aware, of course, of the objections which can be urged against the use of suspensions of leukocytes obtained in this manner. There may well be certain contaminating substances which cannot be freed from the leukocytes even by repeated washings. Nevertheless, it seems to us that the evidence is strong that in human blood the leukocytes have an action similar to that of the blood-platelets in the production of coagulation. It does not necessarily follow that the leukocytes play so important a rôle

as the blood-platelets in producing spontaneous coagulation. In the first place, the platelets outnumber the leukocytes in normal blood, 50 to 1. Again it is a well-known fact that platelets rapidly gather in large numbers at any break in continuity of the vessel walls. Moreover, the peculiar adhesive property of the platelets may well be an important factor.

It has been shown by Delezenne[21] and others that birds' blood which contains no blood-platelets can be kept spontaneously incoagulable if uncontaminated by tissue juice. On the addition of foreign bodies coagulation usually takes place. Morawitz is inclined to believe that the leukocytes contain some substance that assists in coagulation but that it is not so readily available as the similar substance in the blood-platelets. Consequently, until the addition of foreign bodies to the bird's plasma no coagulation takes place.

TISSUE JUICE AS CYTOZYME

The striking effect of tissue juice on coagulation has been recognized since the work of Buchanan[22] in 1845. Following Bordet's experiments we used three specimens of muscle from human beings, three specimens of beef muscle, one specimen of lamb muscle, one specimen of rabbit muscle and one specimen of guinea-pig muscle. Each specimen of muscle was macerated in a mortar with a small amount of physiological salt solution with 0.05 per cent. sodium oxalate. The emulsion was strained through a fine wire mesh. The microscopic examination of this emulsion showed the presence of blood in a few instances. In those instances one cannot be sure of the absence of blood-platelets. Moreover, it is well known that blood platelets tend to clump and stick to the finer capillaries of muscles and the organs after death. It is doubtful even if prolonged perfusion of muscle or of an organ can entirely eliminate the possibility that the blood-platelets are still present.

Using this emulsion of muscles in drop doses, parallel experiments were undertaken to test the relative efficiency of these muscle suspensions in replacing the suspension of blood-platelets. We found that all the suspensions of muscles from various animals were effective in assisting coagulation. The results were not entirely constant but it seemed to be generally true that in the preparations made up with the suspension of human muscle, coagulation took place in practically the same time as when we used the preparation of blood-platelets. There was often a delay of a minute or two (four or five minutes as compared with two or three minutes) when the suspensions of muscle from beef, lamb, rabbit and guinea-pig were used. It was also found that in order to produce throm-

21. Delezenne, C.: Arch. de physiol., 1897, ix, 333, 347.
22. Buchanan, A.: Proc. Phil. Soc. Glasgow, 1845, ii, 16.

bin the suspension of muscles required a longer time of contact with the various other necessary elements than was required of the blood-platelets (nine to fifteen minutes compared with seven minutes).

The suspensions of human muscle resisted heating in exactly the same way as did the suspensions of blood-platelets and the suspensions of leukocytes. These suspensions of human muscle could be heated to 100 C. for fifteen minutes without injury. On the other hand the suspensions of the various non-human muscles became inactive when heated at 100 C. for fifteen minutes. Bordet and Delange working with rabbits found that the suspension of the beef muscle when heated at 100 C. for fifteen minutes was only slightly less effective than the suspension of rabbit's muscle or the suspension of rabbit's platelets, heated in a similar manner.

Experiment 11.—Take seven tubes, A, B, C, D, E, F and G, to each add 0.4 c.c. of recalcifying fluid and 0.1 c.c. of serum. To A add nothing. To B add 1 drop of suspension of platelets, to C add 1 drop of suspension of platelets heated to 100 C., for fifteen minutes. To D add 1 drop of suspension of human muscle; to E add 1 drop of the suspension of human muscle heated to 100 C. for fifteen minutes. To F add 1 drop of suspension of beef muscle; to G add 1 drop of suspension of beef muscle heated at 100 C. for fifteen minutes. After twenty minutes add to each tube 0.5 c.c. of diluted dioxalated plasma. There is no coagulation in A to which no cytozyme has been added. Coagulation takes place in four minutes in B and C, D and F; in eight minutes in E. In G there is no coagulation in four hours but there is a clot the next day. Similar experiments were done with the muscle suspensions of lamb, rabbits and guinea-pigs. These experiments seemed to show that unheated muscle suspension can act as cytozyme, but the heated muscle suspension, except human, have very little action.

This same result can be shown in another way:

Experiment 12.—Take seven tubes, A, B, C, D, E, F and G. To each add 0.3 c.c. of clear oxalated plasma; to A add nothing. To B add one drop of the suspension of platelets. To C add 1 drop of the suspension of platelets heated at 100 C. for fifteen minutes. To D add 1 drop of the suspension of human muscle. To E add 1 drop of the suspension of human muscle heated at 100 C. for fifteen minutes. To F add 1 drop of the suspension of beef muscle. To G add 1 drop of the suspension of beef muscle heated to 100 C. for fifteen minutes. Add to each 1.2 c.c. of the recalcifying fluid. A clots in twenty-four minutes, B and C in eight minutes, D in five minutes, E in eleven minutes, F in twelve minutes and G in eighteen minutes.

Therefore it appears that the addition of the heated suspension of beef muscle hastened coagulation very little, while the other suspensions acted like the suspension of platelets.

Bordet and Delange found the muscle suspensions from animals other than the rabbit, hastened coagulation somewhat, but not so much as the suspension of rabbit's muscle. The result was the same whether the suspensions had been heated or not. They assume a certain amount of specificity in the action of cytozyme. The problem of the specificity of the different constituents which take part in coagulation is much confused. Additional evidence has been introduced by Loeb[8] and

Muraschew[23] which tends to confirm the existence of a certain amount of specificity in the reaction between some of the components of thrombin. Bordet and Delange worked, of course, with material from rabbit blood. To assume that the cytozyme of non-human muscle fails to withstand heating like human muscle because of a specificity in the cytozyme, is very attractive, yet we are not sure that this assumption is warranted. The specimens of the human muscle, obtained in two instances at necropsy, and in one instance from operation, were used very promptly. The preparation of the other muscles was generally delayed several hours at least for unavoidable reasons. There is, then, the factor of the age of the preparations as well as the factor of the different methods of death. Both these factors must be considered. We found no tendency of the muscle suspensions to cause retraction in the clot. Furthermore, as in the case of blood-platelets, neither the suspension of leukocytes nor the suspension of muscle, no matter in what quantity, would of itself cause coagulation of the fibrinogen solution either with or without the presence of calcium.

PEPTONE AS CYTOZYME

Bordet and Delange were able to substitute an emulsion of peptone for the platelet suspension. This emulsion of peptone was effective only when it was of a certain reaction. Of course, peptone is merely digested tissue. We are not aware of the exact method of preparation of the peptone used by Bordet and Delange. We have tried various forms of peptone, Witte's and Merck's peptones and Peptone "Roche." We have tried various degrees of acidity and alkalinity. With the use of Witte's peptone and Merck's peptone the preparations showed a very slight coagulum the next day, while the control showed nothing. Peptone "Roche," which is not made from animal tissue, did not show even this slight activity. We believe that this discrepancy between our findings and those of Bordet and Delange is due to the method of preparation of the peptone. We do not feel that this is an essential part of the work of Bordet and Delange. It seems probable that a peptone prepared under the most favorable conditions, especially in regard to heat, might well give the results obtained by Bordet and Delange. It is of interest, however, that our peptones which were obtained from beef, and in the preparation of which heat was used, gave with the other elements of human blood results similar to those obtained by using a heated emulsion of beef muscle.

Bordet and Delange[24] in a more recent paper have studied further the nature of cytozyme. They have been able to isolate an active principle from muscle juice and from the platelets. This active principle, which can be used in very small quantities as cytozyme, resembles a lipoid and

23. Muraschew: Deutsch. Arch. f. klin. med., 1904, lxxx, 187.
24. Bordet, J., and DeLange, L.: Ann. de l'Inst. Pasteur, 1913, xxvii, 341.

seems to be identical with the lecithin of the muscle and platelets. We have not attempted to confirm these findings, which coincide with the work of Howell,[25] Zak[26] and others.

SUMMARY OF OUR WORK ON CYTOZYME

From our experiments we have been able to confirm most of the work of Bordet and Delange.

We have confirmed the importance of blood-platelets in the process of coagulation. We have studied certain properties of the activity of the platelets. We have shown that *in vitro* leukocytes and tissue juice can replace platelets in the process of coagulation, and have similar properties as the platelets. We have also observed certain results that suggest that the active principle of the tissue juices has a certain amount of specificity in its action.

We find the following discrepancies between our work and that of Bordet and Delange. Human blood-platelets keep their activity even after heating at 120 C. for fifteen minutes.

We find that, *in vitro,* leukocyte suspensions seem to be as active as platelets instead of much less active, as Bordet and Delange found.

We find also, with human blood, that suspensions of muscle other than human lose their activity on heating at 100 C. for fifteen minutes.

We were unable to repeat the work of Bordet and Delange with peptone as cytozyme; this is probably due to the difference of the peptone used.

In addition to the experiments of Bordet and Delange, we have studied the red blood-corpuscles as cytozyme and found that they possess no coagulating acivity.

SEROZYME

Bordet and Delange use the word "serozyme" to denote that substance in the serum which under certain conditions unites with the cytozyme of the platelets to furnish thrombin. Serozyme may be considered as roughly comparable to the thrombogen of Morawitz and the prothrombin of Howell. Yet serozyme is far from being identical with thrombogen or prothrombin.

PREPARATION AND DEMONSTRATION OF SEROZYME

Bordet and Delange find this active principle, serozyme, best in the serum resulting from the defibrination of the recalcified clear oxalated plasma. The exact procedure follows:

Experiment 13.—One c.c. of clear oxalated plasma plus 4 c.c. of the recalcifying fluid clots in approximately thirty minutes. The clot is removed by defibrination and the resulting serum is kept for twenty-four hours and then is the

25. Howell, W. H.: Am. Jour. Physiol., 1912, xxxi, 1.
26. Zak, E.: Arch. f. exper. Path. u. Pharmakol., 1912, lxx, 27.

substance used as serozyme. Take two tubes, A and B; in each place 0.4 c.c. of the recalcifying fluid and 1 drop of the suspension of platelets. To A add nothing; to B add 0.1 c.c. of the serum. After fifteen minutes add to both tubes 0.5 c.c. of the diluted dioxalated plasma; firm coagulation takes place in Tube B; there is no coagulation in A.

It is evident, then, that the serum furnishes some substance which is essential for coagulation, for without this serum no coagulation takes place.

But cumulative evidence shows the substance which is called serozyme either does not exist as such in the blood-vessels or at least it cannot enter into reaction as an element in producing coagulation. Furthermore, serozyme does not exist as such in an available form even in the oxalated plasma.

Experiment 14.—Three tubes, A, B and C, contain each 0.4 c.c. of the recalcifying fluid and 1 drop of the suspension of platelets. To A add nothing; to B add 0.1 c.c. of old serum; to C add 0.1 c.c. of clear oxalated plasma. After fifteen minutes add 0.5 c.c. of the diluted dioxalated plasma; firm coagulation takes place in two minutes in B; there is no coagulation in A or C.

It can be assumed, then, that the oxalated plasma cannot be used as serozyme, yet the absence of serozyme in the oxalated plasma can also be shown by the following experiment:

Experiment 15.—The serum is obtained in the usual way the day before by the defibrination of the clot formed by the mixture of 1 c.c. of clear oxalated plasma and 4 c.c. of the recalcifying fluid. One c.c. of this serum is mixed with 9 c.c. of the recalcifying fluid and is distributed in tubes of quantities of 0.5 c.c. One drop of the suspension of platelets is added to each tube; then at minute intervals after the addition of the suspension of platelets, 0.5 c.c. of the diluted dioxalated plasma is added. In a similar manner 1 c.c. of the clear oxalated plasma is mixed with 9 c.c. of the recalcifying fluid and is likewise rapidly (to avoid coagulation) distributed into the tubes in quantities of 0.5 c.c. and 1 drop of the suspension of platelets added. At minute intervals 0.5 c.c. of the diluted dioxalated plasma is added. We have here used serum and the recalcified oxalated plasma as serozyme under identical conditions. The addition of the diluted dioxalated plasma precipitates the calcium and prevents the formation of any more thrombin. The serum mixture after contact with the platelets for less than five minutes shows no coagulation. After contact from five to ten minutes there is slight coagulation in ten to twenty minutes. Firm coagulation in three minutes is obtained after the serum mixture has been in contact with the platelets over ten minutes. With the plasma mixture, however, there is no coagulation until the plasma mixture has been in contact with the platelets for fifteen minutes, when firm coagulation takes place in ten minutes.

It is evident that the serozyme is not present as such or in available form in the oxalated plasma.

These results can perhaps be best interpreted in the following way: There exists in the blood and in the oxalated plasma an antecedent substance of serozyme which Bordet and Delange call proserozyme. In the first step in coagulation the proserozyme is either changed to serozyme or somehow becomes available as serozyme; then the process of coagulation follows.

THE EFFECT OF HEAT ON SEROZYME

The active principle of serozyme in serum is destroyed by heating at 56 C. for one-half hour. This is in marked contrast to the cytozyme.

Experiment 16.—Two tubes, A and B, contain 0.4 c.c. of the recalcifying fluid and 1 drop of a suspension of platelets. To A add 0.1 c.c. of twenty-four-hour-old serum. To B add 0.1 c.c. of twenty-four-hour-old serum which has been heated at 56 C. for one-half hour. After fifteen minutes add 0.5 c.c. of diluted dioxalated plasma. Firm coagulation takes place in A in two to three minutes; there is no coagulation in B.

The antecedent substance of serozyme in the oxalated plasma is likewise destroyed by heating at 56 C. for one-half hour, as seen in the following experiment:

Experiment 17.—Heat several cubic centimeters of clear oxalated plasma for one-half hour at 56 C. The fibrinogen is precipitated. To 1 c.c. of this heated oxalated plasma one adds 4 c.c. of the recalcifying fluid, but there is no coagulation. The same clear oxalated plasma without heat coagulates in thirty minutes on recalcification. Take two tubes, A and B, to each add 0.3 c.c. of the recalcifying fluid and 1 drop of platelets. To Tube A add 0.2 c.c. of the recalcified heated plasma, to tube B add 0.2 c.c. of twenty-four-hour-old serum. After twenty minutes add 0.5 c.c. of diluted dioxalated plasma; coagulation takes place in two to three minutes in Tube B and there is no coagulation even the next day in Tube A.

THE EFFECT OF BARIUM SALTS ON SEROZYME

Serozyme is absorbed by the action of barium sulphate, and serum treated with barium sulphate is rendered incapable of reacting with platelets. The following is a typical protocol:

Experiment 18.—Take two tubes, A and B, each of which contains 1 c.c. of serum; to A add 6 drops of a thoroughly washed suspension of barium sulphate in physiologic salt solution. To B add 6 drops of physiologic salt solution. After contact for one-half hour, centrifugalize A and pour off the supernatant fluid; then take two tubes, C and D, both containing 0.4 c.c. of the recalcifying fluid and one drop of platelets. To C add 0.1 c.c. from Tube A; to D add 0.1 c.c. of Tube B; after fifteen minutes add 0.5 c.c. of a diluted dioxalated plasma. Tube D coagulates promptly in nine minutes; in Tube C there is no coagulation even after four hours.

Barium salts also absorb the antecedent substance of serozyme in the oxalated plasma.

Experiment 19.—Mix together 30 drops of a thick suspension of barium sulphate in physiologic salt solution, 4 c.c. of the recalcifying fluid and 1 c.c. of clear oxalated plasma. After contact for several hours centrifugalize and decant. The decanted fluid is spontaneously incoagulable plasma containing all the essentials for coagulation except serozyme. This plasma will clot on the addition of serum. Take three tubes, A, B and C, each containing 1 c.c. of the plasma, recalcified and treated with barium; to Tube A add 3 drops of the suspension of platelets; to Tube B add 0.2 c.c. of serum. To Tube C add 0.2 c.c. of serum and 3 drops of platelets. There is no coagulation in Tube A; Tubes B and C clot in about eleven minutes.

Therefore, it may be assumed that barium has a selective action for serozyme and the antecedent substance of serozyme. Once thrombin has been formed, barium has no deterient effect in the process of coagulation.

QUANTITATIVE ACTION OF SEROZYME

Serozyme cannot be used repeatedly in the fashion of an enzyme. This is well shown in the following experiment:

Experiment 20.—Take four tubes, 1, 2, 3 and 4; in Tubes 1 and 2 put 0.6 c.c. of the recalcifying fluid; to Tubes 1 and 2 add 0.4 c.c. of serum. To Tubes 3 and 4 add 0.8 c.c. of the recalcifying fluid and 0.2 c.c. of serum. To Tubes 2 and 4 add 2 drops of any inert substance as physiological salt solution. To Tubes 1 and 3 add 2 drops of the suspension of platelets. After contact over night, the next day the tubes containing the platelets are centrifugalized and the supernatant fluid is drawn off. The fluid in each of the four tubes is divided into equal parts thus giving eight tubes. To one set of four tubes add 1 drop of a thin suspension of platelets, to the other set of four tubes add 1 drop of some inert solution as physiologic salt solution. After contact for fifteen minutes test the coagulating power of the fluid by adding equal amounts of the diluted dioxalated plasma to each of the eight tubes. Coagulation takes place in less than ten minutes in Tubes 2 and 4, to which the platelets were recently added. In Tubes 1 and 3, both with and without new platelets, there is no coagulation until the next day. This is due to the fact that the serozyme had all been used up to form thrombin and there was no remaining serozyme to unite with the recently added platelets to form new thrombin. The coagulation that takes place the next day is due to the feeble thrombin still remaining after being kept over night. In Tubes 2 and 4, which had no platelets, there is of course no coagulation. Therefore it may be argued that serozyme is used up in the production of thrombin and cannot be used again. One also sees in this experiment a fact which has been mentioned before, but which will be dealt with in more detail under the heading of thrombin, namely, that thrombin largely disappears in a given fluid at the end of twenty-four hours. This disappearance of thrombin in twenty-four hours is the reason that serum is kept for twenty-four hours before being used as serozyme. A recent serum, as will be shown, contains a considerable amount of thrombin; this has largely disappeared at the end of twenty-four hours. It is also evident that the more thrombin is formed the more platelets and the more serozyme is used up. It will be shown later that a plasma, rich in platelets, furnishes more thrombin and therefore uses up more serozyme.

Consequently, to obtain a serum yielding the largest amount of serozyme, it is necessary to recalcify the oxalated plasma which has been subjected to a very prolonged centrifugalization, and is on that account very clear and very poor in platelets. The serum obtained from the defibrination of the clot in the recalcified, very clear, oxalated plasma is poor in thrombin and rich in serozyme.

We have shown before that serozyme once used cannot be used again. It is possible to show further that the action of serozyme is a definitely quantitative action. With a given amount of calcium and platelets, a certain amount of serozyme is required in order that thrombin may be formed to coagulate fibrinogen. In rabbits, Bordet and Delange found that the minimum amount of serum containing active serozyme that would react with one drop of the suspension of platelets in 0.4 c.c. of recalcifying fluid and clot 0.5 c.c. of diluted dioxalated plasma was between 0.01 c.c. and 0.02 c.c. In our work on human blood we found that the minimum amount of serum required was between 0.04 and 0.08 c.c. A typical protocol is given:

Experiment 21.—A tube containing 0.04 c.c. of serum plus 1 drop of the suspension of platelets, plus 0.5 c.c. of the recalcifying fluid and left in contact for fifteen minutes and then 0.5 c.c. diluted dioxalated plasma is added. There is no coagulation. If, however, instead of 0.04 c.c. of serum 0.08 c.c. is added and the experiment repeated there is firm coagulation in four minutes.

The amount of serum required to furnish this minimum amount of serozyme depends of course on the content of the serum in serozyme. We have been able to show that the twenty-four-hour-old serum contains varying amounts of serozyme depending largely on the method of preparation. This will be dealt with in more detail under the heading of thrombin. An illustrative protocol follows:

Experiment 22.—One obtains from four different plasmas, four serums as follows: Serum A is obtained from the defibrination of a clot of the recalcified cloudy plasma which has been reinforced by the addition of several drops of platelets. Serum B is obtained from the defibrination of the clot from recalcified cloudy plasma. Serum C from the recalcified clear plasma; Serum D from the recalcified very clear plasma. The next day dilute each of these four serums with the recalcifying solution, 1 : 5, 1 : 10, 1 : 20 and 1 : 50. Then take 0.5 c.c. of each dilution of each of the four serums in separate tubes; add to each tube 1 drop of the suspension of platelets and then fifteen minutes later add 0.5 c.c. of the diluted dioxalated plasma. One finds that there is no coagulation in any of the tubes with the dilutions of 1 : 50. The quantity of serozyme is not enough in any of the serums. Serum A and Serum B do not cause coagulation in dilutions of 1 : 10 or 1 : 20. Serum A causes coagulation in one hour in dilutions of 1 : 5; Serum B in forty-five minutes. On the other hand Serum C will cause coagulation in the dilution of 1 : 5 in three minutes; 1 : 10 and 1 : 20 in ten minutes. Serum D causes coagulation in three minutes in dilutions of 1 : 5, 1 : 10 and 1 : 20. Therefore it is evident that Serum D is much more rich in serozyme and that the serum is capable of assisting in coagulation even in high dilutions.

It is evident that the more platelets in the original plasma, the more serozyme is used up to form thrombin, and the less serozyme is left in the serum after coagulation. This experiment illustrates particularly well the varying strengths of serozyme in the same amount of serum obtained under different conditions, and the importance of using, for recalcification, very clear oxalated plasma, which is very poor in platelets, in order to obtain serozyme.

SEROZYME IN NORMAL HUMAN SERUM

We have also studied somewhat human serum obtained in the usual way and allowed to clot spontaneously. Human serum, after twenty-four hours, shows comparatively little serozyme. Specimens vary, but no specimen showed coagulation in less than one-half hour, though we used amounts as high as 0.5 c.c. of serum with one drop of platelets and 0.5 c.c. of the recalcifying fluid, left in contact for fifteen minutes, and then 1 c.c. of diluted dioxalated plasma added. The obvious deductions from these observations is that in normal blood the relative proportions

of serozyme and platelets are such that the serozyme is almost entirely used up in the formation of thrombin. Consequently, the serum left after the coagulation of blood contains very little serozyme.

SEROZYME IS ATTACHED TO A GLOBULIN

We have studied further the active principle in serum in an attempt to identify it more closely than has been done by Bordet and Delange and other observers. If serum twenty-four hours old is placed in a dialyzer and dialyzed over night in running water, there results a heavy white precipitate. The remaining clear supernatant fluid which one obtains by filtration can be demonstrated to contain serum albumin. In this supernatant fluid no substance which is active in any of the stages of coagulation can be demonstrated. On the other hand, if the precipitate is carefully washed on a filter with a large amount of distilled water and then taken up with a volume either of normal salt solution or of recalcifying fluid sufficient to make up the original volume, this fluid can be shown to possess a similar substance as active as serozyme in approximately the same strength. In other words the precipitate of the dialyzed serum taken up in salt solution seems to contain the same active principle as the original serum. Furthermore, the supernatant fluid of the dialyzed serum seems to contain no serozyme and none of any of the other factors active in the process of coagulation. This observation seems to link this active principle serozyme to the globulins.

SUMMARY OF OUR WORK ON SEROZYME

1. Without serozyme no coagulation takes place.
2. Serozyme is not present as such or in an available form in the circulating blood or in the oxalated plasma.
3. It is best obtained from the serum of the recalcified "very clear" plasma.
4. Serozyme is destroyed by heat at 56 C. for one-half hour.
5. It is absorbed by barium salts.
6. Serozyme does not act as enzyme and a certain minimum amount is required to have any action in a given experiment.
7. Serozyme is probably attached to the globulins of the blood since it can be demonstrated in equal potency in the precipitated globulins of serum as in the original serum. Apparently no serozyme is attached to the serum albumins.

THROMBIN

Since the work of Alexander Schmidt,[27] the view that coagulation is brought about by some active coagulating agent which is not present in the circulating blood, has been generally held. Schmidt called this

27. Schmidt, A.: Die Lehre von den fermentativen Gerinnungserscheinungen, Dorpat, 1876.

agent "fibrin-ferment" and believed it to be a true ferment. Morawitz believes that there is much evidence in favor of the fermentative action of this substance, which he calls also fibrin-ferment. This substance is called thrombin by Howell and by Bordet and Delange; it is not considered by these workers to be a ferment.

In confirmation of the work of Bordet and Delange on rabbits' blood, it has been shown before that thrombin is similarly produced in human blood by the union of two active principles (cytozyme and serozyme) in the presence of soluble calcium salt. Thrombin is the active coagulating agent, and so far as is known, the fibrinogen of blood never coagulates without the agency of thrombin. Bordet and Delange have not isolated the active principle thrombin. It has been isolated by Howell in a somewhat complicated manner. The study of thrombin and its characteristics is somewhat difficult, as it is not present except by the action of serozyme and cytozyme, and furthermore, under ordinary conditions, thrombin rapidly deteriorates.

RAPID DETERIORATION OF THROMBIN

It can be shown that thrombin is present in excess under the usual conditions of spontaneous coagulation. Oxalated plasma, rich in platelets, when recalcified, and salted plasma, when diluted, both develop a greater amount of thrombin than is necessary merely to coagulate the fibrinogen present.

This excess of thrombin, however, rapidly disappears, and after twenty-four hours is present in so small quantities that it can no longer be regarded as an important factor.

This is shown on the following experiment:

Experiment 23.—Five tubes, A, B, C, D and E. Tube A contains 1 c.c. of salted plasma; Tube B 1 c.c. of cloudy oxalated plasma to which additional platelets have been added. Tube C contains 1 c.c. of cloudy oxalated plasma; Tube D contains 1 c.c. of clear oxalated plasma. Tube E contains 1 c.c. of very clear oxalated plasma. To Tube A is added 4 c.c. of distilled water with 0.015 per cent. calcium chlorid; to Tubes B, C, D and E is added 4 c.c. of the recalcifying fluid. Tube A clots in four minutes, Tube B clots in four minutes, Tube C in ten minutes, Tube D in thirty minutes and Tube E in forty minutes. As soon as a firm clot has formed it is defibrinated and one gets Serum A, Serum B, Serum C, Serum D and Serum E. These serums are then tested for thrombin at varying intervals. One mixes equal parts of each serum and diluted, dioxalated plasma; one finds in the case of Serum A that absolutely fresh serum will clot diluted dioxalated plasma in four or five minutes. One hour later this same Serum A requires seven or eight minutes to clot the same amount of the fibrinogen solution. Serum A when twenty-four hours old will form only a feeble clot after twelve hours' contact with the fibrinogen solution. Serum B will clot when fresh an equal amount of the fibrinogen solution in thirty minutes; Serum C when fresh in one hour, Serum D when fresh in five hours, Serum E when fresh in ten hours. These last four serums when kept over night will only show a feeble clot after contact for more than twelve hours with the fibrinogen solution. It is evident therefore that thrombin thus obtained deteriorates rapidly and after twenty-four

hours is almost absent. The serum obtained from blood which has been allowed to clot spontaneously shows the same characteristics. The fresh serum will clot an equal amount of the fibrinogen solution in twenty minutes to one hour. Serum which is twenty-four hours old requires over ten hours to produce a feeble clot in an equal amount of the fibrinogen solution.

THE EFFECT OF VARIOUS SALTS ON THROMBIN

It has long been known that various salts when added to blood prevent coagulation. We have shown above that barium salts interfere with the process of coagulation by their influence on serozyme.

THE EFFECT OF CONCENTRATED SODIUM CHLORID SOLUTION ON THROMBIN

It has already been shown that a sufficiently strong mixture of sodium chlorid and blood will not coagulate. We have also shown that in this mixture coagulation takes place when the salt content is reduced to that of an approximately physiologic salt solution. The serum resulting from the defibrination of the clot contains a large amount of thrombin. Such a serum (as has been shown) contains more thrombin than the serum from the clot which results from the recalcification of oxalated plasma. As will be shown later, this difference is partly due to the harmful effect of the oxalate solution on thrombin. But the difference is probably largely due to the diffusion of the active principle of the platelets in concentrated salt solution, as was shown under the discussion of cytozyme. It is evident, then, that no permanent damaging effect on thrombin or any of its necessary constituents is brought about by the concentrated saline solution. This can also be shown as follows:

Experiment 24.—To two tubes, A and B, add 0.2 c.c. of a 10 per cent. solution of sodium chlorid with four times as much calcium chlorid as is present in the recalcifying fluid. To Tube B add 1.8 c.c. of distilled water. Add to both A and B 0.4 c.c. of serum and 3 drops of platelets. After forty minutes add to A 1.8 c.c. of distilled water and immediately to both A and B 1.5 c.c. of diluted dioxalated plasma. In Tube A in which the mixture of serum and platelets was brought in contact with a concentrated solution of sodium chlorid there is no coagulation. The contact was sufficiently long and just before the fibrinogen solution was added the sodium chlorid solution was restored to the usual physiologic strength. In Tube B coagulation takes place in eight minutes.

We can therefore assume that concentrated solutions of sodium chlorid prevent the formation of thrombin, although all the necessary constituents are present. Just how the concentrated solution of sodium chlorid acts is not apparent.

EFFECT OF CITRATE SOLUTIONS ON THROMBIN

Solutions of sodium citrate prevent the formation of thrombin, as is shown in the following experiment:

Experiment 25.—If 0.2 c.c. of oxalated plasma and 0.1 c.c. of sodium citrate solution 4 per cent. and 0.8 c.c. of the recalcifying fluid are mixed together there is no coagulation. Furthermore, one takes four tubes and each contains 0.3 c.c. of the recalcifying fluid and 0.2 c.c. of serum. To Tube A 0.1 c.c. of sodium citrate solution 2 per cent. is added. To Tubes C and D 0.1 c.c. of physiologic

salt solution is added. Add a drop of the suspension of platelets to Tubes A, B and C. After fifteen minutes add to Tube B 0.1 c.c. of the 2 per cent. sodium citrate solution and add to all four tubes 0.5 c.c. of diluted dioxalated plasma. Coagulation takes place in less than two minutes in Tubes B and C, but there is only feeble coagulation after twelve hours in Tubes A and D. To Tube D no platelets were added and to Tube A the citrate solution was added with the serozyme and cytozyme. In Tube B the citrate solution was added after the formation of the thrombin and coagulation takes place rapidly. Therefore solutions of citrate prevent the formation of thrombin but do not exert any influence on the coagulating power of thrombin already formed.

EFFECT OF OXALATE ON THROMBIN

Oxalate solutions prevent the formation of thrombin by precipitation of calcium salts. Thrombin once formed does not require the presence of calcium in order to coagulate fibrinogen solutions. This has been shown repeatedly. The fibrinogen solution contains sufficient oxalate so that the calcium in the usual solution in which the thrombin is formed is all precipitated and there is an excess of oxalate. On the other hand, there is evidence that coagulation takes place more rapidly if there is a slight amount of free and available calcium when the initial contact takes place between thrombin and the fibrinogen solution.

Furthermore, the presence of oxalate seems to have a harmful effect on thrombin. Bordet and Delange utilized these two facts in the procedure of separate oxalation. The principle of this procedure is the precipitation of the calcium by oxalate after the formation of thrombin, and then, after five minutes' contact between the excess of oxalate and thrombin, the addition of the fibrinogen solution in the form of diluted monoxalated plasma. The proportions used are such that the total amount of oxalate is precisely the same as in the case of the use of the diluted dioxalated plasma as a fibrinogen solution. The only difference is the precipitation of the calcium before the contact between thrombin and fibrinogen. This method is especially sensitive in demonstrating a contrast between fresh active thrombin and an old feeble thrombin. When thrombin is fresh, active and abundant, the fact that it contains no soluble calcium salt when it comes in contact with the fibrinogen solution makes no difference. There is, however, a striking contrast in the case of an old relatively feeble and scanty thrombin. An illustrative protocol follows:

Experiment 26.—Fresh thrombin is obtained by defibrinating the clot of the diluted salted plasma. Take parallel tubes and test equal parts of this serum against an equal part of the diluted dioxalated plasma and also against equal parts of the diluted monoxalated plasma, having in the last instance oxalated the serum, 1 : 1,000. The serum is tested when fresh and at the end of an hour. The fresh serum in each instance causes coagulation in from two to three minutes. At the end of an hour the serum tested against an equal amount of diluted dioxalated plasma requires seven or eight minutes for coagulation. By the method of separate oxalation one to two hours is required.

The rapid deterioration of thrombin and the further weakening of the action of old thrombin by exposing it to oxalate solution and decalcifying it before bringing it in contact with fibrinogen is also shown in the following experiment, in which thrombin is prepared somewhat differently.

Experiment 27.—Many tubes of thrombin are prepared by mixing 0.4 c.c. of the recalcifying fluid, 0.1 c.c. of serum and 1 drop of the suspension of platelets. The thrombin is then tested against 0.5 c.c. of the diluted dioxalated plasma and also by the addition of 0.1 c.c. of sodium oxalate solution, 0.5 per cent, and five minutes later of 0.5 c.c. of diluted monoxalated plasma. The tests are made at varying times. Coagulation under four minutes takes place in the mixtures to which the diluted dioxalated plasma is added until the thrombin is ten hours old. Thrombin twenty-four hours old requires over twelve hours to cause a feeble clot in the diluted dioxalated plasma. In the method of separate oxalation, thrombin up to two hours old requires less than four minutes to clot the fibrinogen solution. The time is gradually lengthened and thrombin twenty-four hours old will cause no coagulation in the method of separate oxalation.

THROMBIN AND SEROZYME IN SERUM

It has been shown that serum twenty-four hours old contains very little thrombin. It is this twenty-four-hour old serum that is used as serozyme. The relation between thrombin and serozyme in serum is interesting. We have shown that both cytozyme and serozyme act in a quantitative manner. It follows, therefore, that in a given blood or plasma with only a given amount of the antecedent substance of serozyme, the more thrombin that is formed from the reaction between the cytozyme and the serozyme the less serozyme will be available in the serum after coagulation and separation of the serum. Therefore, the more thrombin a serum contains the less serozyme is available. This can be well tested experimentally if one controls the amount of thrombin by using varying amounts of platelets. It follows that the fewer available platelets there are to react to form thrombin, the less thrombin will be formed and the more serozyme will remain in the serum. This is well shown in the following experiment:

Experiment 28.—A is oxalated cloudy plasma to which several drops of a thick suspension of platelets have been added. B is oxalated cloudy plasma; C is clear oxalated plasma, D is a very clear oxalated plasma, obtained by prolonged centrifugalization at high speed. One c.c. of each of these plasmas is recalcified by the addition of 4 c.c. of the recalcifying fluid. After coagulation the clot is removed by defibrination and one has Serum A, Serum B, Serum C and Serum D. Each of these serums is diluted one to five and tested for thrombin against an equal volume of diluted dioxalated plasma. A clots in three hours, B in five hours, C in twelve hours and D in twenty four hours. Therefore thrombin is demonstrated to be present in proportion to the amount of platelets used. On the next day Serum A, Serum B, Serum C and Serum D are each diluted with the recalcifying fluid 5 times, 10, 20 and 50 times. Then prepare tubes as follows: Take 0.5 c.c. of each dilution of each serum in separate tubes; to each add 1 drop of suspension of platelets and fifteen minutes later 5 c.c. of diluted dioxalated plasma. The tubes containing Serum D in dilutions of 1 : 5, 1 : 10 and 1 : 20 clotted in two minutes. There was no clot in the dilution 1 : 50 even the next

day. The tubes containing Serum C clotted in less than five minutes in dilutions 1 : 5, 1 : 10 and 1 : 20, but not in dilution 1 : 50 even the next day. The tubes containing Serum A and Serum B showed a slight clot in the dilutions of 1 : 5 in two hours, but no clot in the other dilutions. This shows conclusively that Serum D is poorest in thrombin but much richer in serozyme.

Experiments with fresh serum from ordinary normal blood clotting spontaneously show some thrombin activity, practically none the next day. Such a serum used the next day as serozyme is very weak and somewhat variable. One assumes that the elements furnishing the serozyme are in sufficient abundance to join with nearly all of the elements which we call cytozyme to form thrombin and leaves behind very little unused serozyme.

QUANTITATIVE ACTION OF THROMBIN

Thrombin is not a ferment, and is able to coagulate only a definite amount of fibrinogen. The following experiment bears on this point:

Experiment 29.—Take four tubes, A, B, C and D; each tube contains 0.4 c.c. of the recalcifying fluid, 0.1 c.c. of serum and 1 drop of the suspension of platelets; after 15 minutes we have the formation of thrombin and proceed to test it in various ways. To Tube A add 0.5 c.c. of the diluted dioxalated plasma; this is the classical experiment and coagulation takes place in less than three minutes. To Tube B we add 0.5 c.c. of plasma which has been dioxalated but not diluted. In this case we have the same amount of oxalate but considerably more fibrinogen. Coagulation takes place in eight minutes. Tubes C and D have their calcium precipitated by the addition of 0.1 c.c. of sodium oxalate, 0.5 per cent. Five minutes later add to C 0.5 c.c. of diluted monoxalated plasma and coagulation takes place in eight minutes. To Tube D add 0.5 c.c. of non-diluted plasma, oxalated 1 : 1,000. In this case there was no coagulation. In C and D by separate oxalation the activity of the thrombin was somewhat handicapped and while in C it can coagulate a diluted solution of fibrinogen, this small amount of thrombin in D is incapable of coagulating a strong solution of fibrinogen.

We must, therefore, conclude that thrombin is a definite substance which acts quantitatively and not as a ferment.

TIME REQUIRED FOR THE FORMATION OF THROMBIN

Thrombin is not formed at once by bringing in contact the two active principles cytozyme and serozyme in a favorable calcium medium. The following experiment is illustrative of this point:

Experiment 30.—Take 10 tubes and prepare in each thrombin in the usual way by the mixture of 0.4 c.c. of the recalcifying fluid, 0.1 c.c. of serum and 1 drop of the suspension of platelets. At minute intervals add 0.5 c.c. of diluted dioxalated plasma. There will be no real coagulation in the tubes in which the contact has been under seven minutes; where the contact has been seven minutes or longer there is firm coagulation inside of two minutes after the fibrinogen is added.

Using both the diluted dioxalated plasma and also the method of separate oxalation, the time was fairly constant at about seven minutes in many experiments. It is of considerable interest that Bordet and

Delange, working with rabbits, found that the necessary time of contact was only one and five-tenths minutes. This is one of the variations between human and rabbit blood. Another constant and interesting result of these experiments was that the coagulation was apparently just as rapid and just as firm when the contact was seven minutes as when it was prolonged to twenty or twenty-five minutes. This suggests that the formation of thrombin is delayed for a definite amount of time, but that once begun the formation occurs almost instantaneously. Against this argument is the fact that oxalated plasma which contains many platelets, coagulates in a few minutes (six to ten) on recalcification, while a very clear plasma containing very few platelets requires thirty minutes or sometimes even forty-five minutes, for coagulation on recalcification. It is true that a very weak thrombin requires a considerable length of time for the change of fibrinogen to fibrin, and this may be the explanation of the delay in the case of a recalcified oxalated plasma, poor in platelets. In the ordinary experiments the conversion of fibrinogen into fibrin by a reasonable amount of thrombin takes place rapidly (under two minutes). The time-consuming element in the whole process of coagulation seems to be in the formation of thrombin. The length of time of contact *in vitro* between the various elements necessary for the production of thrombin is about seven minutes in our experimental production of thrombin. This corresponds very closely to the coagulation-time of blood taken from the vein and allowed to clot spontaneously as in the method used by Lee and White,[15] who found the normal coagulation-time to average six and one-half minutes.

It has long been known that temperature has a very marked effect on the time of coagulation. The temperature variation in coagulation-time probably concerns the reaction whence thrombin results.

SUMMARY OF OUR WORK ON THROMBIN

1. Active thrombin formation can be prevented by the presence of concentrated sodium chlorid solution, by sodium citrate, by the absence of calcium and by the presence of barium, which absorbs the serozyme. Once thrombin is formed, however, none of these substances will prevent its action on a fibrinogen solution.

2. It is true, however, that a weak thrombin does not act as well in a medium from which the calcium is precipitated out before the contact with the fibrinogen solution is made. This is shown in the differences between the action of thrombin in the method of separate oxalation and when put in contact with the dioxalated plasma.

3. It has also been shown that thrombin requires a definite amount of time for its formation. This amount of time is considerably longer in human beings than in rabbits.

4. The amount of thrombin is shown to depend on the amount of serozyme and cytozyme used.

5. Thrombin once formed deteriorates rapidly and can barely be demonstrated in the media used in our experiments after twenty-four hours.

6. Thrombin is not a ferment and can coagulate only a certain amount of fibrinogen solution.

7. It has been shown under cytozyme that thrombin can be formed when cytozyme from any of the various sources unites with the serozyme of the blood.

GENERAL SUMMARY

We have been able to demonstrate that the fundamental principles in coagulation as studied by Bordet and Delange in rabbits' blood also hold true for normal human blood.

The differences which we have found are minor ones. We have found that thrombin requires a longer time for its formation in human blood than in rabbits' blood. We have also found that the minimum amount of serozyme required to permit coagulation to ensue is larger in human blood than in rabbits' blood.

We have been unable to confirm the work of Bordet and Delange on the use of peptone as cytozyme. This is probably due to differences in the preparation of peptone.

Although our argument is open to possible objections, we have shown that white corpuscles can be used as cytozyme; they are perhaps not as efficacious as blood-platelets or tissue juice.

We have not been able to employ as cytozome the heated muscle juice of non-human animals in our work on human blood. This is somewhat different from the findings of Bordet and Delange, and tends to confirm their suggestion that there is a certain amount of specificity in the action of the various elements of coagulation.

We have been able to pursue somewhat further than they the investigation of the active principle serozyme and have apparently found it intimately associated with the globulins of the blood.

We have described a modified technic of obtaining human blood which has given very satisfactory oxalated plasma.

99 Commonwealth Avenue—295 Beacon Street.

ULCUS VENTRICULI *

M. H. GROSS, M.D., AND I. W. HELD, M.D.
NEW YORK

PATHOGENESIS

Notwithstanding that a great deal of experimental work has been done to explain the pathogenesis of gastric ulcer, the real etiology is as yet not clear. We, therefore, consider it a duty to analyze the work and theories advanced, and if possible draw conclusions which will somewhat elucidate the subject.

The fact that ulcus rotundum only occurs in the stomach and its immediate vicinity has given rise to the theory that the gastric juice had something to do with the formation of the ulcer, hence the name "ulcus pepticum."

The question soon arose: What is it that really protects the gastric mucosa against autodigestion? Various authors have tried to answer that question by different explanations.

Hunter saw the protective agent of the gastric mucosa against autodigestion in the principle of "life"—i. e., that living tissue cannot be digested.

Claude Bernard[1] contradicted Hunter by experimental proof, inasmuch as he showed that the leg of a living frog is digested in gastric juice.

Pavy[2] attributed the protection of the gastric mucosa against autodigestion to the alkaline blood circulating through the stomach walls.

Stricker[3] saw in the mucus of the stomach a protective agent against the autodigestion of the stomach.

What are the disturbing factors that allow the gastric juice to digest certain portions of the stomach, causing ulcer?

Virchow[4] saw disease of the blood-vessels as a factor, inasmuch as an ischemia is produced, thereby causing disturbance of nutrition and leading to autodigestion.

---

* Submitted for publication Sept. 4, 1913.

1. Bernard, Claude: Leçons de physiologie experimentale, Paris, 1856.
2. Pavy: On Gastric Erosions: Guy's Hospital Reports, 1868, xiv, 464.
3. Stricker: Ueber den Einfluss der Magensaft-Absonderung auf den Chlorgehalt des Harnes, Berlin klin. Wchnschr., 1887, p. 768.
4. Virchow: Historisches Kritisches und Positives zur Lehre der Unterleibs affectionen, Virchow's Arch. f. path. Anat., v, 364.

While O. Cohnheim[5] conceded that there is a local circulatory disturbance, he could not agree that the disease would be primarily in the blood-vessels, because were that the case ulcer would be a more frequent disease in arteriosclerotics; we find, on the other hand, that ulcer is a disease of the young.

Another argument against the theory of local blood-vessel disease is the fact that we so rarely meet with syphilitic ulcers of the stomach, although we know that syphilitics are so frequently subject to endarteritis; the same is also true of those afflicted with tabes dorsalis, who, as we find, frequently have hemorrhages from the stomach without any local ulcers.

The results of animal experimentation in producing secondary injuries and consequently autodigestion of the stomach, are the following:

Schiff[6] intersected the talami and cerebral peduncles, producing hemorrhagic infiltration in the stomach, erosions and even ulcer formation. He explained his results as neuroparalytic hyperemia, caused by injuries to the central vasomotor nerve trunk of the stomach.

O. Cohnheim injected suspension of plumbic chromate into the stomach circulation, by which he succeeded in blocking only the branches of the mucosa and submucosa; at the autopsy he discovered large ulcers with abruptly descending edges and clean bases.

Koch and Ewald[7] caused gastric ulcer by section of the spinal cord, and after that introducing strong hydrochloric acid into the stomach, so causing deep penetrating ulcer.

Ritter[8] and Decker[9] produced ulcer by trauma and thermic irritation. Silberman[10] caused ulcer by producing hemoglobinuria.

The last two explain to us the clinical relation of ulcer in some cases in which hot food is quickly swallowed (cooks), and the ulcer in malaria which is so frequently associated with hemoglobinuria.

Quincke[11] produced ulcer in animals by bleeding them to a severe anemia. (Our clinical deduction of the frequency of ulcer with chlorosis.)

5. Cohnheim, O.: Zur Frage der Selbstverdauung des Magens, Vorlesungen ueber allg., Pathol., 1880, ii, 50.

6. Schiff: Ueber die Gefaessnerven des Magens, Arch. f. Physiol. Heilk., 1854, xiii, 30.

7. Koch and Ewald: Arch. f. exper. Pathol., vol. ii.

8. Ritter: Ueber den Einfluss von Traumen auf die Entstehung des Magengeschwürs, Ztschr. f. Klin. Medizin., xii, 592.

9. Decker: Experimenteller Beitrag zur Etiologie der Magengeschwürs, Berl. Klin. Wchnschr., 1887, p. 368.

10. Silberman: Experimentelles und Klinisches zur Lehre vom Ulcus Ventriculi rotundum, Deutsch. med. Wchnsch., 1886, No. 29, p. 499.

11. Quincke: Die Entstehung des Magengeschwürs, Deutsch. med. Wchnschr., 1882, No. 6, p. 79.

The effect of circulatory disturbance on the development of ulcers of the stomach has also been studied through animal experimentation.

Pannum[12] caused hemorrhagic infarcts and ulcers of the gastric mucosa by injecting an emulsion of wax particles into the central portion of the femoral artery in dogs.

O. Cohnheim[13] produced ulcers in dogs analogous to ulcers in men by injecting a suspension of chromate of lead into the splenic or gastric interior.

Talma[14] caused ulcer by producing anemia in the stomach as a result of faradic irritation.

While the vascular experiments are proof as to ulcer formation in animals, we clinically do not frequently find ulcer of the stomach as a result of emboli or thrombi.

According to D. Gerhard,[15] small ulcers resembling hemorrhagic erosions may be caused by the swelling of ruptured follicles.

Undoubtedly, many superficial ulcerations occur which do not develop into typical ulcers; to this category belong the hemorrhagic erosions of Rokitansky.

That erosions lead to ulcer only in a minority of cases can be proven by the fact that in the circumscribed hemorrhagic areas in the gastric catarrh of alcoholics, in acrobats who introduce sharp bodies into their stomachs, follicular swellings are often found, but no ulcerations.

We see, therefore, that a factor outside of the stomach, either of constitutional origin, like status asthenicus, chlorosis, vagotonia (Eppinger and Hess[16]), or other chronic diseases that would influence the general nutrition, must be causative in the pathogenesis of ulcus ventriculi. This leads us now to the newer and latest work done to establish the above contentions. Before proceeding, however, we must mention the fact that Boetcher and Latulae[17] attribute the causation of ulcer to bacterial invasion. They demonstrated bacteria in colonies on the floor of the ulcer.

Türk[18] produced ulcer by injecting colon bacilli.

Recently the association of ulcus ventriculi with rheumatism, rheumatic endocarditis and tonsillitis has been noted.

---

12. Pannum: Experimentelle Beitrage zur Lehre von der Embolie, Virchow's Arch. f. path. Anat., 1862, xxv, 308.
13. Cohnheim: Pathologie der Verdauung: Vorlesungen ueber allg. Pathol., ii, 22.
14. Talma: Cited from Riegel's "Diseases of the Stomach," 1903, p. 554.
15. Gerhard, D.: Zur Diagnostik und Therapie des runden Magengeschwürs, Deutsch. med. Wchnschr., 1888, p. 74.
16. Eppinger and Hess: Zur Pathologie des vegetativen Nervensystems, Ztschr. f. klin. Med., lxvii, 205, and lxviii, 345.
17. Boetcher and Latulae: Diseases of the Stomach, Hemmeter, 1903.
18. Türk: Experimental Gastric Ulcer, Jour. Am. Med. Assn., 1906, xlvi, 1759.

Stockton[19] introduced a neurotrophic theory:

Agreeing that gastric ulcer occurs on a devitalized gastric mucosa being acted on by gastric juice, what is it that, at such an early age, leads to a devitalized condition, causes ulcer and prevents healing? In his masterful paper he explained the ulcer as a result of a local neurotrophic condition analogous to herpes, indiopathic hematoma, and Raynaud's disease.

The neurotrophic theory excited attention, and R. Dala-Vedora[20] experimented on forty-three animals, excising the vagus and injecting alcohol into the vagus, the celiac plexus and splanchnicus.

In all experiments on the vagus results were negative, while injury of the celiac plexus caused erosions and even necrosis of the gastric mucosa.

Von Yzeran[21] succeeded in producing gastric ulcers in rabbits by cutting the vagus below the diaphragm.

Gunderman[22] attributes the occurrence of ulcus ventriculi to what he calls a disfunction of the liver (disturbed function of the liver), based on the experiments of Friedrich and Engelhard, who produced ulcus by ligating the mesenteric vessels, and those of Payr, who produced ulcus of the stomach by injecting caustic liquids into the vessels of the stomach.

The same authors also found changes of the liver, besides the ulcer of the stomach. Based on that, Gunderman in a number of rabbits ligated the main left branch of the portal vein and found that besides the local atrophy of the liver, there resulted an acute ulcus of the stomach, and in one animal that survived forty-eight days the ulcus adapted all the characteristics of a chronic ulcus pepticum. In some instances even a duodenal ulcer was produced, and in one dog he succeeded in producing an ulcus ventriculi by the same experiment. He concluded from that that normally there are formed toxic substances which, however, by the normally functionating liver cell are rendered non-poisonous. If the liver cells are diseased, this disintoxication cannot be accomplished.

The fact that through injection of liver extract one can produce ulcus ventriculi, or intestinal bleeding, is, according to Gunderman, a proof of the toxic influence of the dead liver cell.

On further investigation the question naturally arises, why do such ulcers only occur in certain parts of the stomach, and why do they heal with such great difficulty?

---

19. Stockton: Etiology of Gastric Ulcer, Med. News, Jan. 14, 1893, p. 34.
20. Dala-Vedora: Experimenteller Beitrag zur Kenntniss der Pathogenesis des Ulcus Ventriculi, Arch. f. Verdauungskr., viii, No. 3, pp. 255 and 411.
21. Von Yzeran: Experimentelles zum Magengeschwür, Ztschr. f. klin. Med., 1901, lx, No. 3, p. 81.
22. Gunderman: Versaml. der Deutsch., Gesellsch. f. Chirurg., Berlin, March 26-9, 1913.

Schuetze[23] bases his theory on the fact that ulcer of the stomach can only result at a point where the mucosa is not properly protected (locus minoris resistentiae). He utilizes as a foundation for his theory the findings of Adolf Schmidt, Lange, Faber and others, who found in certain portions of the stomach an epithelium resembling intestinal epithelium, and that many such cases had achylia during life. Schuetze argues that in cases in which acid is present, the above named epithelium is destroyed, the mucosa not protected, resulting in ulcer. This would also explain why ulcus is more common in the young, because the epithelium is of embryonic origin.

Ashhoff[24] points out that the seat of the ulcer is mostly situated in one of four parts of the stomach. These parts (he speaks of *"Engen,"* i. e., narrowings) are brought about by surrounding organs; near the cardia by diaphragmatic pressure at the antrum cardiacum; lesser curvature, by pressure by the aorta; at the pylorus by the spine; and at the duodenum by the head of the pancreas.

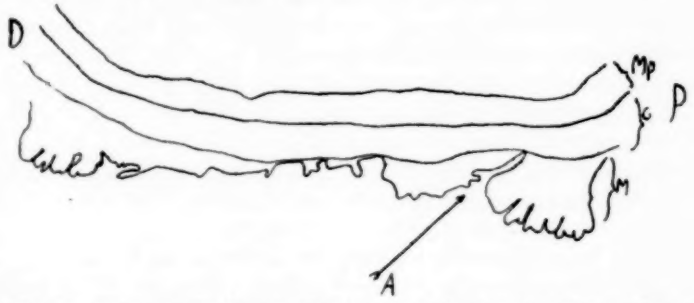

Fig. 1.—Ulcus ventriculi (Aschhof); P, proximal part of the ulcer; D, distal part of the ulcer; M, mucosa; C, connective tissue; Mp, muscularis propria; A, undermined brim of the proximal part and direction of progress of the ulcer.

The flow of the chyme forcing itself through these narrower areas mechanically (according to Aschoff) brings about ulcer formation.

By the same mechanical theory he explains the progress and the characteristic form of ulcer. The chyme passing the ulcerated area has a tendency by its mere force to irritate the proximal brim of the ulcer producing proliferation and thickening, and grinding off the distal part, causing it to appear lower than the proximal part.

The passage of the chyme wave is also held responsible by Aschhoff for undermining the thickened proximal brim and so causing the progress of the ulcer in that direction (Fig. 1).

---

23. Schuetze: Wien. klin. Wchnschr., No. 11, 1912.
24. Aschoff: Lectures, Mount Sinai Hospital, New York, 1913.

We personally are inclined not to accept the theory of Aschhoff that narrowing is responsible for the seat of the ulcer at the points outlined by him.

Firstly, ulcers may be found in almost any portion of the lesser curvature, sometimes more anteriorly, and sometimes more posteriorly.

Secondly, the position of the stomach varies in different individuals (ptosis, vertical position, etc.).

Thirdly, because of the adaptibility of the stomach to pressure influence.

Aschhoff's explanation of the form and progress of the ulcer is more convincing.

Eppinger and Hess, in their brilliant experimental work on the vegetative nervous system (vagus, sympatheticus), show the importance of the influence of the vagus and sympatheticus on the functions of the different organs, and they point out that where the vagus tone of the gastric mucosa is in a state of hyperirritation, that hypersecretion and hyperacidity, as well as spastic contractions of the gastric muscle, lead to ischemia and ulcer formation.

Continuous spasticity prevents the healing of such ulcers. According to Eppinger and Hess, therefore, ulcer of the stomach occurs in individuals with stigmata of vagotonia.

Roessle[25] calls the ulcus ventriculi a "second disease," second to a disease outside of the stomach (appendicitis chronica; cholelithiasis; chronic obstipation), which by way of the visceral nerves causes contractions of the musculature of the stomach, thus leading to ischemia and ulcer formation.

Lichtenbelt[26] through his numerous experiments advances the explanation that ulcus is the outcome of spastic contractions of the muscularis mucosa, not the muscularis propria, thereby constricting the blood-vessels and causing ischemia and ulcer. As an underlying factor he considers the neuropathic predisposing element essential.

Eppinger and Hess, Roessle, and Lichtenbelt, have stimulated von Bergman[27] to advance the theory of the so-called "spasmogenic ulcus pepticum."

Von Bergman holds that, on account of spastic contractions of the muscularis mucosa, the local blood-vessels become obstructed and the mucosa digested.

---

25. Roessle: Das Magengeschwür eine zweite Krankheit, Mittheil. Grenzgeb., xxv, 4.

26. Lichtenbelt: Ulcus Ventriculi, Gustav Fischer, 1912.

27. Von Bergman: Das spasmogene Magengeschwür, München. med. Wchnschr., 1913, No. 4, p. 169.

According to Boeninger and others (*Verein f. innere Medicin*, March, 1913) spastic contractions lead not only to ischemia, but also to hemorrhages of small blood-vessels.

The prevention of healing and further tendency to chronicity is due, according to von Bergman, to continuous spastic contractions of the muscularis. These contractions are the result of an underlying neuropathic tendency, and he cites fifty-eight out of sixty patients with ulcers who showed neuropathic stigmata of the vagosympaticus type.

To show how much attention has of late been paid to the general status as a predisposing factor to ulcus ventriculi, we cite the theory of E. Stoerk,[28] who considers the status lymphaticus an important factor in the etiology of ulcus ventriculi. Those affected with general lymphatismus, Stoerk says, likewise have an increase in the lymphatic element in the stomach; their follicles are more readily irritated and respond with an état mameloné (a marked increase in follicles) which serves as a mechanical hindrance. Besides that he also states that those that are of the status lymphaticus have likewise disturbances of the vegetative nervous system, and that they are predisposed to bacterial infection, hence the difficulty of the healing of the ulcer.

In spite of all the theories and experimental work enumerated thus far, coming from such conscientious and painstaking observers, and really throwing so much light on the subject, from a clinical aspect one does not feel that all the requirements are covered in explaining the pathogenesis of ulcus ventriculi.

We shall attempt, therefore, to analyze the origin of ulcer as the result of a mechanical disturbance of the stomach. In order to develop our views, we shall have to dwell somewhat on that part of the anatomy of the stomach most concerned with the mechanical power of the stomach, i. e., the musculature.

The musculature of the stomach consists of the muscularis of the stomach wall proper—muscularis propria—and the muscularis of the mucous membrane—muscularis mucosa.

The muscularis propria consists of two layers—an outer layer, formed by the longitudinal fibers, and an inner layer, formed by the circular fibers. The longitudinal fibers coming down from the esophagus, run along the small curvature in a more compact manner to the pylorus, while these fibers on the lateral wall of the stomach, as well as on the fundus, are distributed relatively thinly and apart from each other. On the greater curvature and at the pars pylorica the longitudinal fibers are again somewhat more defined where they appear in more continuous and

28. Stoerk, E.: "Ulcus und Lymphatismus," Deutsch. med. Wchnschr., 1913, No. 11, p. 496.

compact manner; part of them go to the first part of the duodenum, most of them terminate in the sphinctor pylori.

The circular fibers of the esophagus appear in stronger bundles in the region of the cardia, and in thick distribution at the small curvature, spreading out more thinly to the fundus and the rest of the stomach, until they reach the pylorus, where they form a strong ring—the sphinctor pylorii.

The so-called fibrae obliquae which all anatomists at first considered a part of the innermost circular fibers, running obliquely from cardia to fundus, and spreading toward the fundus, are considered by the Swedish anatomist, A. Retzius,[29] not as a part of the circular fibers, but as a separate third and innermost layer of muscle fibers, characteristic of the stomach only, and not found in any other part of the gastro-intestinal tract.

The fibrae obliquae lie like a muscular belt around the left side of the cardia (see Fig. 2) from where they spread to the front and back wall of the stomach, continuing to the antrum pylori.

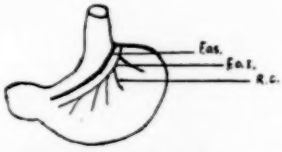

Fig. 2.—Schematic drawing of the stomach; F. o. s., fibrae obliquae, pars superior; F. o. i., fibrae obliquae, pars inferior; R. c., rami communicantes.

They ride, as it were, on the cardia and continue to a small part of the esophagus.

To explain the physiological function of the fibrae obliquae, we must accept with Willis an upper, more horizontal part of the fibrae obliquae, strongest at the cardia and in the region of the lesser curvature, and a more oblique part, which runs along the lateral wall of the stomach, ending at and dipping into the pylorus ring, and communicating by short branches with the circular fibers of the muscularis propria of the stomach. The function of the fibrae obliquae, according to R. Kauffman,[30] who calls it "horse-shoe loop" (Fig. 3) is to bring the upper part of the anterior and posterior wall of the stomach in the region of the lesser curvature nearer to each other. According to A. Retzius the upper horizontal part of the fibrae obliquae forms by its contraction a groove

29. Retzius, A.: Bemerkungen ueber das antrum pylori beim Menschen und einigen Thieren, Arch. f. Anat. Physiolog., 1857, p. 74.

30. Kauffman, R.: Anatomisch experimentelle Studien ueber die Magenmuskulatur, Ztschr. f. Heilk., 1907, xxviii.

(as in ruminating animals) along the lesser curvative, which, depending on innervation, close at regular intervals and more or less tightly.

The function of the lower bundle of the fibrae obliquae, due to their rami communicantes with the circular fibers of the stomach musculature, and their collaboration, is to cause local contractions of the stomach (*"loculamente"*) identical with and serving the same purpose as the intestinal segmentations (Cannon). These bundles, by their peculiar distribution, form the connecting link between the pars pylorica and the Retzius groove on one hand, and the fundus on the other. In this manner liquid and solid food substances can pass through the groove—with the exclusion of the fundus proper—from the esophagus directly to the pars pylorica, and backward by way of antiperistalsis from the sphinctor pars pylorica toward the esophagus.

This antiperistalsis has been proven by W. Beaumont,[31] Cannon[32] and O. Prym.[33]

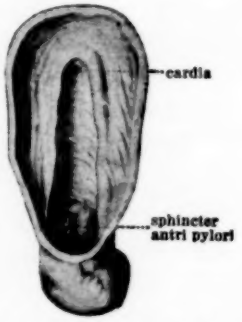

Fig. 3.—"Retzius Groove" (R. Kaufmann, Ztschr. f. Heilk., 1907, xxviii).

We therefore see that the musculature of the stomach is thickest and strongest at the pylorus—3½ mm. Next to that, the lesser curvature and cardia—1½ mm. and more, and thinnest at the fundus—1 mm., and in some parts 0.4 mm.

It is evident from the distribution of the musculature that the stomach can safely be subdivided into two compartments, one corresponding to the fundus (corpus), and the other to the pylorus and lesser curvature (Kauffman[30]). The fundus with its poorly developed musculature may be compared to the auricle, while the pylorus and lesser curvature with its strong musculature, is comparable to the ventricle of the heart.

31. Beaumont, W.: Neue Versuche ueber den Magen Saft. Translated by B. Luden, Leipzig, 1834, p. 75.

32. Cannon, W. B.: The Movements of the Stomach, etc., Amer. Jour. Physiol., 1898, p. 359.

33. Prym, O.: Die Entleerung des Magens, die Trennung des Festen und Fluessigen, das Verhalten des Fettes, Münch. med. Wchnschr., 1908, No. 2.

In contradistinction to the opinion that the Retzius groove is functionally a part of the fundus, we will try to show that the Retzius groove works partially in conjunction with the pars pylorica.

When we now consider the motor function of the stomach according to the experiments of Cannon, Hoffmeister and Schutz,[34] Moritz,[35] Sick,[36] Gruetzner,[37] we see that the greater part of the work of the stomach is done by that compartment where the musculature is most developed, i. e., pyloric part and small curvature. Rieder, Rosenthal and Kaessle[38] showed kinematographically how the pylorus and lesser curvature work harmoniously more actively than the fundus and interchanging with it. The mode of the motor function of the stomach is as follows: As food passes down the esophagus, reaching the cardia, it is then first driven into the fundus (Figs. 4 and 5) where it is knitted by

Fig. 4.—Empty stomach (His); Ac, antrum cardicum; Pc, plica cardiaca; Ppa, plica pancreatica; Pp, pars pylorica; Ap, antrum pyloricum. (Nasse and Brecker, Arch. f. Anat., 1905.)

the peristaltic action of the fundus. The food impregnated with the gastric juice drops down, as it were, into the antrum pylori, which is opened at that stage.

The acid food now excites chemically and mechanically the pars pylorica, causing it to contract, by which contraction part of the food, fit for the duodeum, is allowed to pass through, while coarser particles of the food are, by virtue of antiperistalsis, driven back along the Retzius groove and lesser curvature, to be worked on again and subsequently to be dumped into the fundus (Beaumont).

34. Schutz: Ueber die anatomischen Bewegungen des Magens, Arch. f. exper. Pathol., 1886, xx, 1.

35. Moritz: Studien ueber die motorische Thaetigkeit des Magens, Ztschr. f. Biol., 1896, xxxii, No. 7, p. 313.

36. Sick: Untersuchung ueber die Saftabsonderung des Magens, Deutsch. Arch. f. Klin. Med., 1906, lxxxviii, 1908; xcii, 169.

37. Gruetzner: Studien ueber Magen-Bewegung, Arch. f. Physiol., 1905, cvi, 416.

38. Rieder, Rosenthal and Kaessle: Cong. f. inn. Med., 1909.

The reason we have dwelt somewhat at length on the anatomy of the musculature of the stomach and the motor function is, because it seems to us that there is a direct relation between the strength of the musculature and the location of the ulcer. The mechanical demand made almost exclusively on the antrum pylori and the groove along the lesser curvature explain, in addition to the chemical and thermic irritants, the predisposition of those parts to ulcus ventriculi. The burden laid on the parts just mentioned is doubled if the peristaltic function of the stomach (fundus, corpus) is weakened (atony, dilatation, ptosis).

What is it now, that causes the ulcer formation in these particular regions?

We have learned with certainty that in order to have an ulcer formed, occlusion of the local blood-supply with ischemia (small hemorrhages) and autodigestion is necessary. For the purpose of making our position

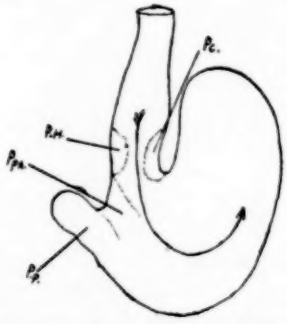

Fig. 5.—Full stomach (His); Pc, plica cardica; Ppa, plica pancreatica; Ph, plica hepatica; Pp, pars pylorica. (Hasse and Brecker l. c.).

clear we shall have to review briefly the mode of production of such ischemia, according to the most recent and most plausible views.

Eppinger and Hess see the occlusion of the blood-vessels in the vago-sympaticus disturbance, causing spastic contractions of the musculature of the stomach on the blood-vessels, occluding them, causing ischemia.

Roessle also traces the origin of the ulcer to a disease outside of the stomach (appendix, gall-bladder) causing spastic contractions by way of the vagus.

Von Bergman (spasmogenic ulcus ventriculi) is practically in full accord with the views of the three above named authors.

Lichtenbelt demonstrated most conclusively that the contraction of the muscularis mucosa is responsive to irritants with the most violent contractions, occluding blood-vessels and causing ulcerations.

All this shows us conclusively that all previous embolic and stagnation theories have no standing.

We are now to prove how we perceive the origin of the ulcer, based on the views of these authors.

In individuals of the vagus-sympatheticus type, where the vagus symphatheticus disturbance manifests itself chiefly in the stomach, we first encounter a secretory disturbance in the form of increased acidity or increased secretion when symphatheticus elements predominate, diminished secretion when the vagus phenomena predominate always, however, in the form of digestive disturbances. The patient reduces his diet in order to relieve his symptoms, resulting in hypotony; or, he may have a congenital status asthenicus with an inborn hypotony. In the state of hypotony we know, through the studies of Cannon and the Roentgen ray, that the peristole of the stomach is disturbed, or almost abolished.

Excessive work is now thrown on the musculature of the propulsive mechanism of the pylorus and lesser curvature, the food arriving there chemically and mechanically in an unprepared state. For some time the musculature, by an excessive contraction, accommodates itself. Finally comes a time when, in that part (pylorus, lesser curvature) of the musculature most irritated, more than ordinary contractions—really tetanic contractions—take place, contracting on the local blood-vessels, causing ischemia and autodigestion, and leading to ulcer.

What happens if an erosion is once formed? Small, superficial erosions are protected against chemical and mechanical irritation by the spastic contractions of the muscularis mucosa, and heal with minute-scar formation, without giving rise to any marked symptoms during life. But if the erosions are multiple, or the involved area is more extensive from the start, the protection just mentioned will not suffice; spastic contraction will give way to more continuous tetanic contraction, including the muscularis propria, causing more marked symptoms and pain.

These pains serve as a warning, which, if the patient observes a spare diet, may lead to a cure; if, on the other hand, he does not heed the warning, or at the slightest improvement goes back to errors in diet and habits, the continuous irritation prevents healing of the ulcer and aids its progress.

Roessle, as stated, considers ulcer of the stomach a secondary disease to chronic appendicitis, cholelithiasis, etc., and so, by way of the nervous system, causing spastic contraction of the musculature of the stomach, with resulting ischemia and ulcer formation.

While we consider it an established clinical fact, and it has been proven by the Mayos and others conclusively, that ulcus ventriculi is frequently associated with the above-named diseases, we feel, however, that the formation of the ulcer is not by means of the nerves causing the spasms in the musculature of the stomach, but the cause of ulcer formation lies in the stomach itself.

We find that a certain hypersensitive class of people, due to the fact that they have some chronic visceral disease, reduce their diet to a minimum out of fear of pain. From the standpoint of their nervous status the gastric secretion is disturbed, and the same vicious circle occurs here that causes the ulcer on the vagus-symphatheticus basis, viz., peristole almost abolished, on account of the weakness of the fundus muscle, which first gives way to hypotony. The food reaches pylorus chemically and mechanically unprepared, causing greater strain on the pyloric muscle, from where it is thrown back to the Retzius groove along the lesser curvature, where the musculature is most developed, causing abnormal contraction, etc., occluding the blood-vessels, which causes ischemia and autodigestion.

From the fact that some of those suffering with appendicitis, floating kidney, etc., have chiefly gastric disturbances, and that with the removal of the underlying factor the gastric disturbances subside, we can see that functional disturbances of the stomach, secretory and mechanical in type, precede the ulcer formation.

Were the ulcer formed through the nerves causing the spasm of the stomach musculature, as Roessle sees it, we would meet much more frequently than we ordinarily do individuals with ulcer of the stomach.

Given numerous individuals afflicted with the above-named diseases and still never acquiring ulcer of the stomach, how is that to be explained? It seems to us explainable in the following manner: Individuals of the sthenic type, without the stigmata of vagus symphatheticus, have the symptoms of the underlying disease only during the attack, but their condition is not made intolerable by the reflex gastric secretory disturbances which lead to under-nourishment and finally hypotony.

Other direct predisposing factors that play a part in the production of ulcer, like chlorosis, secondary anemia, and malaria, must also have their origin chiefly in the mechanical and secretory disturbances; but here we may have in addition the disease in the vessels themselves (Virchow) predisposing to ulcer.

By far the least frequent ulcers, on the anterior or posterior wall or fundus, have their origin mostly in trauma, either from without (shoemakers; corsets) or from within (cooks; alcoholics).

Sex: It has traditionally come down to us in text-books that females are more prone to ulcer than males. Recently Smithies[39] and Bamberger[40] rightfully pointed out that this is not the case and, corresponding with our experience, that men are even more affected than women.

39. Smithies: Gastric Ulcer without Food Retention, Am. Jour. Med. Sc., March, 1913, p. 340.

40. Bamberger: Ulcus Ventriculi, Hirschfeld, Berlin, 1910.

Age: Ulcers occur mostly between the ages of 15 and 40; with females, in the earlier years and males at later age.

Syphilitic and tuberculous ulcers are caused by the specific virus. In the syphilitics we really find the gummatous, or fibrous tissue formation or ulcer, corresponding to syphilitic affections in other parts of the body.

Up to this point we have endeavored to outline our view of the seat, cause and progress of the ulcer.

What is the cause of the spontaneous healing of ulcus simplex? According to Katzenstein, Blum and Fuld,[41] ulcus ventriculi is the consequence of some circumscribed injury of the stomach wall, which does not heal because the normal proportion of pepsin and antipepsin have been upset, more pepsin being secreted, while there is less antipepsin than normal.

J. Kauffman[42] called our attention to the fact that in hyperacidity and ulcus the mucous secretion in the stomach is increased; he further showed that according to the investigations of Schuetz, Pawlow and Landauer, the mucus has a protective property against the chemical, thermic and mechanical influences on the ulcer. On that the silver nitrate treatment (to be mentioned later) is based, in order to excite mucous secretion when such is necessary. This according to Kauffman, prevents the progress of the ulcer.

Later observers like von Aldor,[43] Schuetz,[44] and the experimental work of Türk,[45] confirm Kauffman's hypothesis that the healing of ulcer depends on increased mucous secretion.

MORBID ANATOMY

The round ulcer macroscopically looks as if stamped out with a die, with characteristic round, sharp outline, of various sizes. The greatest loss of substance is in the mucosa. In old ulcers the muscularis is pulled up to the mucosa. Occasionally the ulcus takes in the whole wall of the stomach, causing marked thickening. This thickening with the seat at the pylorus may simulate a tumor; it is hard and hence its name, callous ulcer. Some ulcers become penetrating, and adherent to neighboring organs. Ulcus penetrating through anterior wall forms a perigastritis. Ulcus penetrating through posterior wall causes adherence of the stomach

41. Katzenstein, Blum and Fuld: Experimentelles zur Entstehung des Magengeschwürs, Arch. f. klin. Chirurg., Berlin, ci, No. 1, p. 1.
42. Kauffman, J.: Mangel an Magen-Schleim: Arch. f. Verdauungskr., 1907, p. 616.
43. Von Aldor: Beitrag.. zur pathologie der Magenschleim Absonderung, Berl. klin. Wchnschr., 1909, Nos. 18-19, pp. 826 and 882.
44. Schuetz: Berl. klin. Wchnschr., 1909, No. 27, p. 1253.
45. Türk: Further Observations on the Etiology and Diagnosis of Peptic Ulcer, Brit. Med. Jour., 1907, No. 20, p. 922.

to pancreas. The same may also be true with ulcer at the lesser curvature with adhesions spreading to the pancreas, as one of our cases proved at operation. Adhesions from the pylorus to the gall-bladder are frequent occurrences.

Perforations occur, and these are most frequent when the ulcer is on the anterior wall. If perforation should occur in the region of the pylorus, a localized subdiaphragmatic abscess may form. This abscess may bore its way through into the thorax, forming a pyopneumothorax. Perforation may also occur into any of the neighboring organs.

Microscopically, in a fresh ulcer we see most of the destructive process in the glandular tissue and mucosa. In older ulcers the glandular cells are seen contracted; the cells are sometimes not to be recognized; a few tubules are seen to have undergone cystic degeneration; and a round-cell infiltration is seen in the interstitial tissue of the glands. In still older ulcers connective tissue predominates.

Fig. 6.—Kidney-shaped stomach.

SYMPTOMATOLOGY

Is there such a thing as acute ulcer?

Bolton[46] classes ulcer as acute where the patient suddenly has a severe attack of pain, nausea and hemorrhage; recovering from that he may be free from an attack for the rest of his life, or sometimes another acute seizure may occur. Bolton and others (cited in his article) found post-mortem scar formation where the history had only pointed to one attack. He also counts sudden perforation without previous symptoms to be that of acute perforating ulcers. A case of perforation of gastric ulcer operated by L. Buerger occurred in a man who never had any gastric symptoms before.

Before leaving the subject of what has been described as acute ulcer, we must not lose sight of the fact that acute symptoms and even perforations may occur in chronic ulcers, only the patients who have the ulcer are of the hyposensitive type and hence ignore their symptoms. It is our duty, therefore, even in trivial complaints of the stomach, to follow

46. Bolton: Further Observations on Pathology of Gastric Ulcer, Proc. Royal Soc., 1910, lxxxii, 253.

E. Libman's method, viz., to go over the sensory status of the patient very carefully. Like Libman, we had best test the sensibility by pressure on the tip of the mastoid. Very sensitive people cannot stand the slightest pressure; normal people will stand a moderate degree of pressure; in the hyposensitive class even the strongest pressure causes no discomfort.

We repeat that in such people with slight gastric symptoms, we should weigh the history most carefully, and even where one or two symptoms speak for ulcus ventriculi, we should give him the benefit of the doubt, and thus prevent the disastrous acute perforation or milder complications.

PRE-ULCEROUS STAGE

Before we go into the discussion of the symptoms of chronic ulcer, we consider it essential to briefly state some of the symptoms that we clinically class as a pre-ulcerous stage.

By a pre-ulcerous stage we understand a symptom-complex of vague gastric complaints such as a sensation of fullness immediately after meals, belching and sour eructation, various degrees of pyrosis, and, after heavier meals or psychical emotion, real attacks of pain.

We see such symptoms in girls of the age of puberty, in travelers who take their meals irregularly, quick eaters, hearty eaters and those of the status asthenicus type, or those suffering from chronic appendicitis, etc. Such patients are diagnosticated as having ulcus ventriculi by some, others consider them nervous. We feel, as already hinted at in the etiology, that the symptoms are really due to the progressive secretory disturbances, and the spastic contractions giving way to tetanic contractions. Hence we see that in the pre-ulcerated state the pain does not occur at regular intervals after meals, but depends more on the quality, quantity of food and the psychical emotion which in turn influence the secretory and functional conditions of the stomach. In such cases, prophylactic measures, hygienic and dietetic treatment, will completely do away with the symptoms and prevent ulcus formation.

SYMPTOMS OF SIMPLE ULCER

The symptoms depend a great deal on the size of the ulcer. A small-sized ulcer heals completely, with post mortem findings of a scar where, during life, there were absolutely no symptoms, or the symptoms were of such a vague nature that they escaped diagnosis. We explain the course and absence of symptoms in these small ulcers as stated above, by the contraction of the muscularis mucosa on the diseased surface, protecting the affected area from mechanical and chemical irritants. Possibly also the simultaneous mucus secretion neutralizes the acidity and directly protects the ulcerated area.

If, however, a larger area is involved, where the protective agents do not suffice, we get the more pronounced symptoms of ulcus ventriculi. The first symptom that annoys the patient is the pain. To what is this pain due? And has the seat of the ulcus any influence on the time of occurrence of the pain?

We are fully aware that of late a great deal of importance has been attached to the assumption that pylorospasm causes pain. Glaesner and Kreuzfuchs[47] considered the pain entirely due to a reflex from the duodenal juice stimulating the pylorus to contraction, and hence they speak in ulcus ventriculi of two periods of pain, the early and late pain. The former, they explain, occurs just as soon as the food comes into the stomach, as there is a reflex action of the duodenal juice on the pylorus, opening up the pylorus, allowing the food to pass through; the pylorus then closes (chemoreflex, Pawlow) until the food is more alkaline.

In ulcer, according to the above-named authors, although the stomach is at rest during that time, the pylorus is in spasm, and hence the pain. On the same basis they explain the late pain.

Does this correspond to the clinical picture? We must decidedly answer, No!

First of all, in non-complicated ulcer, we never see an immediate pain after meals; just the reverse, the patient is relieved after taking food. Only spicy and irritating food may cause immediate pain by virtue of mechanical and chemical irritation or causing hypersecretion. We explain the pain of a simple ulcer as being due to mechanical and chemical irritation of the ulcerated area, causing spasms in the form of tetanic contractions of the muscularis mucosa and muscularis propria wherever the ulcer is situated.

As to the time of pain, we know through erroneous text-book traditions that the time varies according to the seat of the ulcer; that is to say, if at the cardia, the pain is immediately after meals; if at the lesser curvature, one-half to one hour after meals; if at the pylorus or duodenum, two or three hours after meals.

This, however, does not correspond to clinical observations. We know that the occurrence of pain is in the majority of cases not dependent on the seat of the ulcer. Before we attempt to explain our reasons for the time in which the pain occurs, we will illustrate our findings with two cases.

ILLUSTRATIVE CASES

Case 1.—A. U., aged 37, laborer; previous history negative, also family history. No status asthenicus. Present complaint dates back to two years before admission to the Har Moriah Hospital, when the patient began to have severe attacks of pain three hours after meals, relieved by taking milk or alkalies. Pain

47. Kreuzfuchs: Ueber den Pylorospasmus, München. med. Wchnschr., 1913, No. 11, p. 582.

was diffused all over the abdomen, radiating to the back, and sometimes, but not always, relieved on vomiting. Physical examination disclosed pressure-pain in the epigastrium; otherwise negative.

Tube on empty stomach, after a night meal of rice and currants, showed absolutely no food residue either macro- or microscopically, no blood, only an increased gastric secretion — 80 with a free acid of 40.

Ewald's test breakfast, removed one hour afterward, showed well chymified contents two-thirds fluid and one-third solid (hyper-secretion), free acid 60, total acidity 80. No blood in stomach contents, and no occult blood in the stools after frequent examination.

Roentgen ray examination immediately after a bismuth meal showed the stomach in a high state of contraction (hypertonic), with the cardia and pylorus drawn to each other (Fig. 6), the significance of which will be described in the division Roentgen-ray Diagnosis of Ulcus of the Stomach.

Such a form has been observed before by Schmieden and termed "snail" form. When it occurs the ulcer is usually at the lesser curvature. Our case was confirmed at the operation (L. Buerger) as an ulcer of the lesser curvature. According to time of occurrence of pain, the seat of the ulcus would have been thought to be at or even beyond the pylorus.

CASE 2.—A. K., married, belt maker. Negative previous and family history. His history of gastric disturbance dates back ten years. For the last three years he had suffered from severe attacks of pain, three or four hours after meals, relieved on taking food or alkaline powders. He never vomited, but had frequent regurgitation. One year ago he was treated in a hospital where he underwent a regular ulcer cure. After that he was comfortable for a few months, when the attacks became more frequent, always severest three to four hours after meals; in addition he had some annoyance from real pain, more or less constant. He was admitted to our service in the Har Moriah Hospital and the physical examination revealed the following:

Status asthenicus, chest negative, tender over epigastrium, but no direct pressure point. On empty stomach (after a meal of rice and currants the night before) we found 10 c.c. gastric juice, which neither macro- nor microscopically showed any food particles. Ewald's test breakfast removed one hour later showed three-fourths solid, one-quarter liquid. Chemical examination showed free acid 10 and total acidity 25 (sub-acidity). No blood; stools showed on two occasions occult blood, and after that every examination of the stools was negative.

On account of his sub-acidity, the continuous pains, the long duration of the disease and the marked emaciation, a suspicion of malignancy arose, and we utilized the Gluczinsky[48] method. This consists of giving to patients who show an an- or subacidity after Ewald's test breakfast, a Riegel's test meal. If, after this test meal, acid secretion is stimulated to an increase, it speaks for ulcer. In our patient, after the Riegel's test meal, the acidity was markedly increased.

Fluoroscopically an ulcus hour-glass contraction of the stomach was seen, which, according to Haudeck, is indicative of an ulcer of the lesser curvature. Because of the continuous pains and his non-yielding to treatment, adhesions were also considered, and surgical interference advised. At the operation (L. Buerger) an ulcer at the lesser curvature was found, spreading to the posterior wall of the stomach and adherent to the pancreas.

This case, too, well demonstrates the fact that the time of pain would have been a misleading factor in localizing the ulcer. We see, therefore, that the time of occurrence of the pain depends on a number of factors; size of ulcer, quality and quantity of food, and whether one or the other

48. Gluczinsky: Differential diagnose zwischen Ulcus Ventriculi und Carcinoma ventriculi, Ztschr. f. klin. Chir., 1912.

ostium of the stomach is sympathetically involved in aggravating the pain. After a light meal, independent of the seat of the ulcer, the pain occurs one to two hours later; after a heavier meal, three to four hours later. This goes to show that in the early course of digestion, when the stomach is full, the ulcerated part of the stomach is protected by the musculature contracting over it; if the stomach becomes empty, relaxation over the ulcerated area sets in, the eroded surface is then exposed to the food and gastric secretions, and hence the pain. In light meals where such is the case, after one or two hours the pain occurs at that particular period; after heavier meals where it takes three or four hours for the stomach to empty itself, the pain occurs later. In stomachs of marked atony, or gastrectasia, we know from experience that the pain occurs even later than three or four hours, even after five or six hours, and is often relieved after vomiting a little food.

More information about the localization of the ulcer gives us the direction in which the pain radiates and in what position the patient has most pain. It is a clinical fact that pain radiating more to the right of the umbilicus speaks for ulcer near the pylorus; pain radiating to the left hypochondrium speaks for ulcer on the lesser curvature. With the ulcer at the cardia there are often attacks simulating left intercostal neuralgia.

As to the influence of position on the seat of the ulcer, we often find that a patient with an ulcer in the region of the pylorus is uncomfortable when he lies on the right side, the opposite being true with the ulcer at the cardia.

Pressure-points in localizing the ulcer (the Boas pressure-point between the tenth and twelfth dorsal vertebra to the right, if ulcer is in the pylorus; to the left, if on the lesser curvature; the painful pressure-point in the epigastrium or the painful pressure-point in the epigastric region, especially when the ulcer is on the anterior wall, or a perigastritis, complicates the ulcer) have only a limited value in establishing a diagnosis or localizing an ulcer.

Einhorn's thread with bucket for determining the location of the ulcer consists in letting the patient swallow a bucket attached to a thread and left over night. When withdrawing, we note whether the thread is stained red, and measure the distance from the teeth. This method does not seem plausible for the following reasons: (1) Because not every ulcer necessarily bleeds; (2) even if it does, it is a question whether the thread will even be touched by that part of the stomach where the ulcer is situated.

A very important aid in localizing the ulcer is the x-ray examination, to be described later.

PYROSIS

Pyrosis was always explained as being due to acids — organic or inorganic — in the stomach. returning along the lesser curvature to the cardia, and with simultaneous opening of the cardia the sour fluid entered the mouth (regurgitation).

Clinically, pyrosis is the result of the excessive production of acids in the stomach, introduced into the stomach with the food, or of eating such foods as tend to increase the acids of the stomach, while at the same time the neutralizing agent, viz., the mucus in the stomach, is not produced in proportion to the acid. We can well picture the pyrosis to be the paresthesia of the stomach. Pyrosis does not manifest itself only in the region of the cardia, but with the patient on the right side, the pyrosis is intensified on the right side, and when the patient is on the left side the pyrosis is stronger at the cardia and lower part of the esophagus. Pyrosis is an important symptom in the pre-ulcerous state, and during all stages of ulcer. It is relieved either by taking alkalies or by vomiting, which tends to prove that the excessive acid is mostly responsible for the pyrosis.

ACIDITY

An increase in the free HCl and total acidity have been considered to constitute an important symptom of ulcus ventriculi. It was even thought that excessive hydrochloric acid was essential in bringing about the ulcer. To-day we know that the gastric juice is non-essential to the production of ulcer, and everything being equal, ulcus may be even produced with a gastric juic of a normal acidity or even of subnormal acidity. However, as we have already learned from the etiology that ulcus ventriculi frequently occurs in individuals that have a tendency to hyperacidity, this may explain why in a great majority of cases of ulcus we frequently find hyperacidity.

In Mayo's clinic, Smithies found hyperacidity in the majority of 140 cases operated on for ulcus; he also found that the free HCl was highest when the ulcus was at the pylorus, while the total acidity was highest when the ulcus was at the lesser curvature on the anterior wall.

Clinically, we find many cases which show hyperacidity during some stage of the treatment, later changing to subacidity and rarely even to anacidity. Notwithstanding a low acidity, the patient has the discomfort of hyperacidity.

H. Strauss[49] termed such cases anacida hyperacida, which he attributed to hyperesthesia of the mucous membrane.

---

49. Strauss, H.: Die Dietbehandlung des Magengeschwürs, Jahreskurs. f. aertzl., Fortbild., August, 1911, p. 55.

We believe that the mucous secretion which serves as a protecting agent against the irritative property of the gastric juice is diminished, and hence even a low acidity tends to produce discomfort.

Riegel explains the diminution of acidity, where there was hyperacidity before, as due to the gradual exhaustion of the acid secretion. In cases of ulcus where we find subacidity, we are sometimes inclined to doubt the existence of ulcus, or suspect carcinoma on the basis of ulcer. To determine this, Gluczinsky[48] gives us a very important clue. Where patients have a subacidity with Ewald's test breakfast, he subsequently gives a Riegel's test-meal, and if he finds the acidity increased, he considers it characteristic of ulcer.

HYPERSECRETION

Strauss and Bamberger[50] consider hyperacidity and hypersecretion as depending on the same source. We find clinically that hypersecretion is even more frequent in ulcus ventriculi than hyperacidity. At times hypersecretion may be intermittent; at other times we can only bring about a hypersecretion after the patient partakes of food. Such a form of hypersecretion is correctly termed by Strauss alimentary hypersecretion. The so-called continuous hypersecretion that Reichmann described as an independent disease, is more frequently an expression of ulcus ventriculi, or ulcus duodeni.

A functional continuous hypersecretion is only of a transitory nature. Gluczinsky called attention to the fact that when there is a hypersecretion the sodium chlorid in the urine is diminished or absent.

NAUSEA AND VOMITING

Smithies has found vomiting in ulcus ventriculi more frequent than have other clinicians. In simple ulcer discussed here, vomiting is infrequent and not a constant symptom. If vomiting occurs it usually relieves the pain. The vomiting of simple ulcus is not the result of the ulcus, but it is more characteristic of certain individuals, who with any pain, especially abdominal, are easily subject to nausea and vomiting. A symptom much more frequently met is regurgitation of sour fluid, causing a burning sensation under the sternum and in the throat, and also a sour taste in the mouth.

HEMATEMESIS

Various authors have given the frequency of hematemesis in ulcer as varying between 30 and 60 per cent. Here A. Jacobi's statement is correct, that statistics differ according to whether we deal with hospital material, or ambulatory or private patients. Certain it is that hemat-

50. Strauss and Bamberger: Fortschritte auf dem Gebiete der Magenerkrankungen, Jahreskurs. f. artzl., Fortbild., March, 1913, p. 42.

emesis is not a frequent symptom. More frequently we find blood coming through the tube. This differs from the blood due to trauma and adherent to the tube, which is bright red and in streaks, while the blood coming through the tube and characteristic of ulcer is fluid, dark red and mixed with gastric juice, sometimes in quantity of 5 to 10 c.c. When we find this we should be cautious with the future use of the tube.

Hematemesis is characterized by a preceding nausea, marked discomfort in the epigastric region, a feeling of extreme weakness, dimness of vision, and finally hemorrhage. The blood is usually dark, mixed with stomach contents, acid in reaction.

To differentiate the hematemesis between an ulcus ventriculi and carcinoma ventriculi, in the latter the blood mixed with the mucous stomach contents is alkaline, having more the appearance of coffee-grounds and may have a decomposed odor; above all we are guided by the cachexia of the patient, because carcinomatous stomachs bleed, as a rule, profusely in the last stage of the disease, due to the ulceration of the carcinoma. (Microscopical examination may disclose cancer cells and the Boas-Oppler bacillus.)

Hematemesis may occur as a result of cirrhosis of the liver, seldom in the course of decompensated endocardial diseases due to congestion; or to atheromatous changes of the stomach blood-vessels or rupture of small aneurysms of the stomach vessels, as a result of arteriosclerosis, and is differentiated by the history of the case and general findings.

A characteristic case of hematemesis as a result of atheromatous changes of the stomach blood-vessels observed by us is worth citing.

CASE 3.—A butcher 57 years of age was admitted to the Har Moriah Hospital in a state of confusion, with a previous history obtained from his family of his suffering a few months before from severe pains behind the sternum. Within a few days the mental symptoms disappeared without leaving signs of any organic nervous disease. He then developed symptoms of intermittent claudication of both lower extremities. With the subsidence of these symptoms abdominal symptoms (angina abdominalis) came to the fore. One year later, with the repetition of the abdominal symptoms, he had severe gastric hemorrhages lasting for a few days. It is now a year and a half since those hemorrhages occurred, and outside of his occasional attacks of angina pectoris he is absolutely free of gastric symptoms.

Other causes of hematemesis not originating in the stomach are: varicosities of the esophagus, small aneurisms of the esophagus, sometimes pulmonary hemorrhages when part of the blood is swallowed, blood coming from the pharynx or nose.

A case of hematemesis as a result of having swallowed blood from an ulcer of the nose was so severe that for four or five days we kept the patient absolutely quiet as a matter of precaution, on suspicion of ulcus ventriculi. Local cauterization of the nose stopped the bleeding and quick recovery followed.

Hematemesis occurs in blood-diseases like pernicious anemia, purpura hemorrhagica and very frequently in "Banti's disease" (splenic anemia).

Vicarious hematemesis replacing menstruation is not infrequent. Cases are cited in which hematemesis repeated itself without any appreciable cause. Charcot drew attention before to this kind of hematemesis. He called it hysteric. We had occasion to observe two such cases in the Har Moriah Hospital — two young girls who had repeated hemorrhages from the stomach, while before and after the hemorrhages they were absolutely free from gastric symptoms. A characteristic feature in both cases was the fact that the hemorrhage was preceded by a state of nervous excitement—flushed face, choking sensation in the throat, no nausea, but marked restlessness.

The cause of hysteric bleeding (Charcot) has never been satisfactorily explained.

Other causes of hematemesis are the bleeding of post-epileptic seizures and injuries to the brain.

In conclusion, we especially call attention to the fact that certain food-stuffs may be vomited that simulate blood; in such cases chemical and microscopic examination will clear up the diagnosis.

OCCULT BLOOD

Another very important symptom to which we should pay careful attention is the repeated finding of occult blood in the stool. We should, however, exclude bleeding from other sources—the gums, pharynx, hemorrhoids, fissures or ulcerations in any other portions of the intestines, and according to Kehr, an ulcerated gall-bladder. The patient should be put on a meat-free diet for at least three days before examination for occult blood. It is certain that occult blood is more frequent in duodenal ulcer than in gastric ulcer.

The repeated finding of occult blood, notwithstanding a perfected ulcer cure, should awaken our suspicion of carcinoma (Elsener). Boas even says that without occult blood no diagnosis of ulcer should be made. With this we differ. We only agree with Boas that where occult blood persists it indicates that the ulcer is in a florid state. It should be mentioned here that as a result of the prolonged oozing a marked secondary anemia may result, sometimes making the patient appear so cachectic that a suspicion of malignancy may arise.

MOTILITY DISTURBANCE

An additional symptom of less frequent occurrence and far less reliable in simple ulcer of the stomach is microscopical stagnation on an empty stomach, after the patient has received rice and currants the night previously. Other authors advise 2 grams of bismuth with the meal of

the preceding night, with the idea that the bismuth will stick to the eroded surface and be found the next morning on an empty stomach.

The delay in emptying the stomach is not, according to our opinion, pathognomonic of ulcus ventriculi. If the ulcer is at the pylorus, there is a delay in emptying the food, due to the associated pylorospasm, and individuals who, irrespective of ulcer, have hypo or atonic conditions of the stomach musculature, have delayed motility irrespective of the seat of the ulcer.

We agree with L. Bamberger,[51] who, in a number of cases in H. Strauss' clinic, found occasional microscopical stagnation in absolutely normal stomachs, and there was no microscopical stagnation in ulcers of the stomach. The Roentgen ray examination has taught us that the stagnated food lies in the neighborhood of the ulcer, corresponding to the local contraction.

COMPLICATED ULCERS

If the ulcer progresses, affecting the serosa, the symptoms vary, depending on the seat of the ulcer.

The most serious complication is that of perforation. The onset is acute, with severe pain in the region of the stomach, sometimes described by the patient as a sensation that something tore in the stomach. There is a marked distention of the abdomen, due to the escape of air and stomach contents, obliterating liver and splenic dulness. General peritonitis develops very quickly, usually within ten to twelve hours in the majority of cases.

There is never vomiting, a characteristic point to which Traube first called attention.

It is very seldom that general peritonitis does not follow, and this is the case when perforation takes place on an empty stomach.

Perforation through the front wall may form a localized abscess anteriorly, which is diagnosed by the palpable mass and the septic temperature. Or it may perforate posteriorly, giving rise to a subphrenic abscess (pyopneumothorax subphrenicus, Leyden). There is flatness of the lower part of the chest and the characteristic three zones described by E. Roth: flatness below the diaphragm, an area of tympany above, and above this another area of flatness due to compressed lung tissue.

The septic temperature, the examination of the blood and aspiration will clear up the diagnosis.

Less frequent forms of perforation deserve mention. A case is described by Osler,[52] where the perforation occurred into the left ven-

51. Bamberger, L.: Ueber die diagnostische Bedeutung alimentaerer Restproben bei ungestoerter Magen Motilitaet, Arch. f. Verdauungskr., 1911, xvii No. 3, p. 241.

52. Osler: Carcinoma of the Stomach, Univ. Med. Magazine, Philadelphia, 1894-5, p. 248.

tricle, and the patient lived for two days. The perforation closed with the systole and opened with the diastole.

A case is cited by Fr. Miller,[53] in which perforation occurred into the lung and the patient coughed up particles of food.

Perforation into the colon is sometimes observed, or perforation into the portal vein, causing pyelophlebitis. Carl Wegele observed a case in which perforation had taken place into the urinary bladder. Perforation into the mediastinum with emphysema of the skin may occur. A perforation observed by Murchinson between the stomach and the left hypochondrium, through the ribs, formed a fistula.

ADHESIONS

A very frequent and important complication is the spreading of the ulcer, becoming adherent to other organs. The symptoms of adhesions depend on where the adhesions have taken place. Adhesions around the pylorus may so twist the pylorus as to cause stenosis. Adhesions of pylorus and gall-bladder give rise to stasis in the gall-bladder and jaundice. Adhesions to the pancreas may give rise to disturbances of the pancreatic function.

Above all, our suspicions as to adhesions should be awakened when the symptoms of the ulcer become aggravated, pains are continuous, and the patient does not yield to the ulcus cure. The aid of the Roentgen ray in the diagnosis of adhesions will be discussed later.

ULCUS VENTRICULI CALLOSUM

In old ulcer, as a result of connective tissue formation and small-cell infiltration, a marked thickening results, involving smaller or greater portions of the stomach. Depending on its location, the symptoms differ. A callous ulcer at the lesser curvature may not give any more characteristic symptom than any other chronic ulcer. The diagnosis is based on the Roentgen ray findings, to be described. If such callous formation is at the pylorus, the symptoms of progressive pyloric obstruction with gastrectasia set in.

It would lead us too far to give a special description of pyloric obstruction, but a few characteristic points, due to obstruction caused by a callous ulcer at the pylorus, should be mentioned.

Clinically, such a stenosis is characterized by marked chronicity. Usually we first obtain a history showing the illness to be of comparatively short duration, with absence of marked pain. The chief complaints are frequent vomiting, usually of comparatively small masses, loss

53. Miller, Fr.: Ulcus rotundum pepticum, Eulenburg Real. Encycl., Ed. 4, viii, p. 834.

of appetite, eructation of sour and offensive odor and marked feeling of distention.

On examination we find the tongue coated; over the abdomen, well below the umbilicus, there is a marked splash, visible peristalsis (stiffening of the stomach, Boas). Introduction of the stomach-tube reveals a marked stagnation.

It takes some time at one sitting, and with the patient in different positions, to wash out the stomach completely. The stagnated food is usually acid; microscopically sarcinae are found.

When we question further into the history the patient confesses to having had pains years before, that make us think of ulcer as a causative factor. On palpation, a tumor is sometimes felt in the region of the pylorus.

An ulcus callosum at the cardia is less frequent and gives rise to symptoms of obstruction at the cardia, with difficulty in deglutition, dilatation of the esophagus above the obstruction, early vomiting of undigested food which is alkaline and mixed with mucus.

A case of callous ulcer is described by F. Sasse,[54] where the callous formation had occupied the greater part of the stomach, and where Roentgenologically there was, in place of the stomach, a narrow shade, and width of the thumb, running from esophagus to pylorus.

A very frequent and important complication is the so-called "hour-glass contraction" of the stomach. It is caused by cicatricial tissue formation, localized either near the pylorus or in the median line, or sometimes near the cardia.

The cicatricial tissue divides the stomach into two compartments which communicate with each other by a canal of varying size.

The diagnosis is aided by the history and by inflation of the stomach, which shows the organ divided into two compartments. Another aid in diagnosis is lavage of the stomach by the sudden reappearance of food particles after the lavage water has returned clear before.

A most important and decisive aid in the diagnosis is repeated Roentgen ray examination showing the constriction always at the same place.

ROENTGEN RAY EXAMINATION

In no other pathological condition of the gastro-intestinal tract is it so necessary that the clinical examination precede the Roentgen ray examination as in ulcus ventriculi.

Simple Ulcer of the Stomach.—In 1906, Hemmeter reported cases of simple ulcer diagnosticated skiagraphically by the bismuth sticking to the eroded surface after the entire bismuth meal had left the stomach.

54. Sasse, F.: Ulcus ventriculi totale callosum, München. med. Wchnschr., 1913, No. 12, p. 650.

Since then Jonas, Jolasse, Holzknecht, Haudek, Groedel, Faulhaber, von Bergmann, Rieder in Germany, and Pfahler, Cole, Jaches, T. S. Hirsch and Skinner in this country, have contributed greatly to the diagnosis of ulcer by means of the Roentgen ray.

Based on the work of those mentioned and some of our own experience, we will study the ulcer by means of Roentgen ray to determine the kind of ulcer, seat of same and whether complicated.

In simple ulcer, Jonas called attention to the fact that we can locate the seat of an ulcer by pressing the stomach while the patient is being fluoroscoped, and at the point where the patient complains of pain. It is essential that the seat of pain should change on deep inspiration, with the change of the position of the stomach.

A more exact method is the determination of the motility of the stomach, by the time the stomach empties itself. According to Holzknecht, whenever an ulcer is associated with hyperacidity, it matters not

Fig. 7.—Ulcus callosum of small curvature.

whether the ulcer is at the pylorus or a distance from the pylorus, there is a delay in motility by virtue of pylorospasm. Rieder and Faulhaber take exception to that view. They believe, and this coincides with our own experience, that motility disturbance on account of pylorospasm speaks for an ulcer near the pylorus, unless there is an associated atony of the stomach, in which case there would be motility disturbance independent of the seat of the ulcer.

Simple ulcer near the cardia gives the picture of cardiospasm. Its rare seat at the greater curvature or posterior wall is so far inaccessible to Roentgen ray diagnosis.

Ulcus Callosum (Chronic small-cell infiltration around the edges of the ulcer).—This form of ulcer is fortunately most commonly situated at the lesser curvature, hence accessible to x-ray diagnosis.

Haudek called attention to the "niche" (nische) symptom characteristic of that form of ulcer. It shows a spot of bismuth on the lesser curvature which empties itself when the stomach is empty. If situated at the pylorus, it interferes with the emptying of the stomach (Fig. 7).

Penetrating ulcers (Fig. 8) are characterized by separate sacks of bismuth with their own air-bag (*Magenblase*) on top.

In the classical article by Holzknecht[55] rules for diagnosis of ulcer are so masterfully laid down that we deem it appropriate to describe them in full.

Based on the fact that whenever there is an ulcus ventriculi there is also a slow emptying of the stomach due to hyperacidity and spasm at the pylorus, and that the sensitive pressure-point is changeable with the position of the stomach either by massaging with the hand while fluoroscoping, or making the patient retract his abdomen while fluoroscoping, the following rule was laid down: Small rest after six hours, sensitive pressure-point changing with the motility of the stomach, no morphological change; conclusion, simple ulcus ventriculi.

Holzknecht and Handell have shown that, where there is antiperistalsis or where the pars pylorica lies to the left, or where there is a snail-form of the small curvature, retraction of the small curvature,

Fig. 8.—Penetrating ulcer.

transverse stretching of the great curvature, the "niche-form"—all these indicate different stages of ulcus and different complications. Based on the above-mentioned signs, the following rules were laid down by Holzknecht: Small rest after six hours; accompanying sensitive pressure-point; pars pylorica situated high and to the left; snail-form of the lesser curvature; conclusion; old contracted ulcus on the lesser curvature at pars pylorica.

Another rule: Small rest after six hours; accompanying pressure point at pars media with a sense of resistance; pars media transversely; "niche-form" without air chamber; conclusion, callus ulcer at the lesser curvature, pars media.

HOUR-GLASS CONTRACTION OF THE STOMACH

In hour-glass contraction of the stomach we should differentiate "x-ray" hour-glass contraction (Fig. 9), persistent hour-glass contrac-

55. Holzknecht: Roentgenologisches ueber Magen-Erkrankungen, Jahreskurs. f. artzl. Fortbild., August, 1911.

tion due to fibrous tissue formation dividing the stomach into two distinct sacs (Fig. 10); spastic hour-glass contraction, and depressions on the greater curvature by tumors or gas in the splenic flexure simulating an hour-glass stomach, and carcinoma of the great curvature simulating hour-glass contraction.

The so-called "x-ray" hour-glass contraction of the stomach is the result of a deep florid ulcer situated at the lesser curvature. The meal passing the ulcerated area causes a contraction of the circular muscle fibers of the stomach, bringing about an indentation of the greater curvature of the stomach.

Watching such a patient take his meal fluoroscopically, we observe the following: The first few spoonfuls slide directly down to the lower sac, at the same time causing the above-described contraction of the curvature so that the rest of the food gathers in the upper sac. This contraction may last from a few seconds to one-half hour; then the stomach relaxes again. This is the reason why such a contraction is not

Fig. 9.—Roentgen-ray hour-glass contraction.

found on the operating table, because under narcosis, and on an empty stomach, there is no contraction.

Under rare circumstances the longitudinal fibers contract, with the ulcer on the lesser curvature, drawing the pylorus and cardia nearer to each other and the entire stomach upwards and to the left. Schmieden and Haertel have termed such a stomach "tobacco pouch stomach." Holzknecht calls it snail form.

A case observed by us, and confirmed on the operating table (L. Buerger) had the form of a kidney-shaped stomach (Fig. 6). An hour later the contraction relaxed and the stomach adopted its normal shape.

The persistent hour-glass contraction shows skiagraphically two distinct sacs separated by a narrow canal.

Jolasse, Rosenfeld, Jonas and Holzknecht conclusively proved the existence of an hour-glass contraction by first giving the patient bismuth milk, then introducing the stomach-tube and watching the progress of the tube in the stomach. If the tube folds up and deviates to the left, it is considered as characteristic of hour-glass contraction.

In neurotics with spastic tendencies an hour-glass contraction may result, but relaxation occurs after the administration of atropin sulphate, 0.0005 to 0.001 subcutaneously. The hour-glass contraction caused by tumors from without is chiefly characterizel by the displacement of the stomach to the other side, and in order to make a diagnosis we must look at the stomach with the patient in a different position, so that the location of the tumor changes, and thereby exercises no pressure on the stomach.

Perigastritic inflammation may simulate hour-glass contraction.

Franz Groedel cites a case, with demonstration of a photograph, where Rieder's meal distinctly showed two parts — one about the middle of the greater curvature and the second at the antrum pylori. Massaging did not influence the condition. Half an hour later the same stomach was found completely filled and of normal shape. Groedel explains this as follows: The perigastric adhesion does not allow the part of the stomach involved in the adhesion to yield to food as rapidly as the other part of the stomach.

Fig. 10.—Hour-glass contraction of the stomach (anatomical).

Carcinoma at the greater curvature, simulating hour-glass, is differentiated by the ragged appearance of the involved part of the stomach due to a defect of filling.

Haudek also succeeded in differentiating an hour-glass contraction due to ulcer from one due to carcinoma. The former is characterized by a transverse stretching of the stomach, and the constriction is chiefly at the lesser curvature; the latter lies longitudinally, the constriction being mostly on the greater curvature; both walls are usually irregular.

For larger sized tumors of the stomach region the Roentgen ray is only important in determining whether or not the tumor belongs to the stomach proper, which is proven by giving Rieder's meal; if the tumor belongs to the stomach, it will be found that a part of the stomach-shadow is missing.

Pyloric obstruction is characterized skiagraphically by marked peristaltic waves.

Adhesions between stomach and liver show the stomach transversely situated and pulled to the right, with absence of the cap and diminished peristalsis.

DIAGNOSTIC CONCLUSIONS

After our lengthy description of the symptoms of ulcus ventriculi, the question arises: In the majority of cases is a positive diagnosis of ulcus ventriculi possible, and on what do we chiefly base our diagnosis?

Our answer is that it is possible in a great number of cases, but we must always base our diagnosis on a number of factors, and likewise consider the general status of the patient, because, in full accord with von Bergman, patients with status asthenicus are more prone to ulcer.

To enumerate: Pain and hypersecretion, even when existing alone and persistently, are positive proof of ulcus ventriculi. And when these symptoms are present in individuals with status asthenicus and nervous symptoms, so much more reason for the diagnosis of ulcus ventriculi (von Bergman).

Von Bergman is right when he considers the nervous stigmata of the status asthenicus as characteristic of ulcus ventriculi. Our clinical experience teaches us that most of the other nervous symptoms disappear when the ulcer is developed. Hence our conclusions are as follows:

Status asthenicus with nervous symptoms varying in nature, sometimes gastric, at other times cephalgic, or neuralgias of other parts of the body—no ulcer. Status asthenicus with most of the other nervous symptoms subsiding, gastric symptoms, particularly pain and hypersecretion, coming to the fore — ulcus ventriculi has developed.

In hyposensitive people the pain is not a predominating symptom; here continuous hypersecretion alone, or tendency to hyperacidity plus frequent dyspeptic symptoms, is sufficient to establish the diagnosis of ulcus ventriculi. The diagnosis is strengthened when occult blood is repeatedly found, other sources of bleeding excluded. Roentgen-ray diagnosis, as already described, is in some cases a positive clue as to the existence and location of ulcer.

DIFFERENTIAL DIAGNOSIS

The disease from which it is most difficult and sometimes almost impossible to differentiate ulcus ventriculi is ulcus duodeni. We shall, therefore, try first to name the symptoms of ulcus duodeni according to Moynihan,[56] the Mayos,[57] and Bier,[58] and see whether they are characteristic of ulcus duodeni only, or are also found in ulcus ventriculi.

56. Moynihan: Correlation of Symptoms and Signs in some Abdominal Diseases, Brit. Med. Jour., 1912, Nos. 1, 3, 4, 5, p. 344.
57. Mayo, W. J., and C. H.: Brit. Med. Jour., 1912, No. 17.
58. Bier: Chirurgische Behandlung der Magengeschwüre, Berl. klin. Wchnschr., 1912, p. 368.

Moynihan considers hunger-pain, relieved on taking food, hypersecretion; pain occurring about four hours after a meal, not relieved by vomiting but by taking some food, and the pain more to the right of umbilicus, as characteristic of ulcus duodeni.

Notwithstanding this statement, made by such an authority as Moynihan, we meet clinically with exactly the same symptoms and still the ulcer is even a distance to the left of the pylorus.

In cases in which only the above-named symptoms are present, a differential diagnosis is not possible, and is often made ad operationem, only as outlined by Mayo, i. e., to be guided by the pyloric vein. If the ulcer is to the left of this vein, the disease is in the stomach, if to the right the ulcer belongs to the duodenum.

One point that aids in differentiating is the fact that the symptoms of ulcus duodeni are more prone to appear in certain seasons (winter) of the year. Another characteristic is that even with severe hemorrhages from stomach and bowels as a result of duodenal ulcer, with the subsidence of the symptoms there may be years of freedom, and then a recurrence of the trouble.

Persistent occult blood in the stools speaks, in our opinion, more for duodenal than for gastric ulcer.

Another aid in the diagnosis of gastric ulcer is the Gross duodenal tube. When the tube is in the region of the ulcer, small blood-particles may be seen in the aspirated contents.

Robust individuals have more duodenal ulcer than gastric ulcer. This may explain why duodenal ulcer was considered more prevalent in men than in women.

Of more importance is the painful pressure point, or hammer percussion point (Mendel), which is the point midway between the angle of the ribs and the umbilicus; and Seyferath[59] considers rigidity of the right upper rectus muscle a characteristic symptom.

The occurrence of perforation, not preceded by gastric symptoms, is more frequent in duodenal than in gastric ulcer.

Finally, the Roentgen-ray findings may aid in diagnosis, inasmuch as in duodenal ulcer, notwithstanding the hyperacidity and hypersecretion, there is no motility disturbance, and we have on the contrary, as in achylia, a hypermotility, and invariably see the first portion of the duodenum full.

A differential diagnosis as to whether an ulcer belongs to the duodenum or to the pylorus is so important because the ultimate result

59. Seyferath: Ueber das duodenalgeschwuer, Berl. klin. Wehnschr., 1911, No. 15, p. 852.

is so different. At the pylorus the frequent progress is toward scar formation with symptoms of pyloric stenosis, while in the duodenum, due to the thinness of the wall, if the disease progresses perforation results; hence in the latter, if medical treatment is not quickly successful, surgical intervention ought to be advised.

To differentiate between a benign and malignant stenosis is essential, when a palpable mass is detected as belonging to the pylorus.

The points which direct us are the following:

Benign	*Malignant*
Marked chronicity with a history of having suffered intermittently for years.	Of more recent date.
Marked gastrectasis.	Slight dilatation; sometimes even a contracted stomach.
Appetite variable.	Almost absent in every case.
Stiffening and peristalsis (Boas) marked.	Very little, or none at all.
Emaciation with anemia.	Cachexia.
The stagnated contents are acid and show sarcinae, or yeast fungi and an acid odor.	Achylia, Boaz-Oppler bacilli and offensive odor.

A very important way of differentiating between benign pyloric stenosis and mere pylorospasm has been pointed out by Holzknecht,[60] by means of the Roentgen-ray examination.

He experimented with papaverin (Merck) and found that in contradistinction to morphin it does not enhance peristalsis and that it hastens emptying of the stomach by about one-third the time. This is accomplished by the property of papaverin to relax circular and longitudinal muscle fibers.

Holzknecht gives patients who show marked stagnation one-fourth to one-half grain of the drug a half hour before the Rieder bismuth meal. In cases in which the stenosis is superinduced by spasm, which is frequently true in benign stenosis, the stomach empties itself much sooner after the administration of papaverin; while in cases of pure pylorospasm the stomach empties itself in due time.

Other diseases that may give rise to difficulties in differential diagnosis we shall only mention, i. e., cholelythiasis, chronic appendicitis, renal colic, chronic pancreatitis and gastric crises.

---

60. Holzknecht and Igollitzer: Papaverin zur Rontgenologischen differential Diagnose zwischen Pylorospasm und pylorus Stenose, Münchem. med. Wchnschr., 1913, No. 36.

The differential diagnostic points between acute hemorrhagic pancreatitis and acute gastric perforation are the following:

Acute Pancreatitis	*Gastric Perforation*
Onset: Sudden.	Usually preceded by gastric symptoms.
Pain: Severest in upper quadrant of abdomen, rigidity localized in the same place.	More diffused; rigidity generalized. Liver and splenic dulness obliterated. A sensation as if something has torn.
Vomiting: Very frequent.	Not frequent, or even absent (Traube.)
Shock: Not marked.	Very marked.
Collapse: More pronounced from the start.	With the development of peritonitis.

ULCUS CARCINOMATOSUM

The development of cancer on the basis of ulcer was at first estimated by Wilson and MacCarty to be about 71 per cent. The studies of Aschhoff and Friedenwald[61] emphatically contradict such frequency. Friedenwald's statistics in 1,000 cases show positively 9 per cent., and 16 per cent. where the relation of ulcer to cancer is of a doubtful nature. Aschhoff's figures are still lower, and according to him, whenever ulcer is found associated with cancer, he considers cancer the primary disease. From a clinical standpoint we are much more inclined to agree with the lower figures.

To diagnosticate the disease where the cancer occurs on the base of the ulcer is of the greatest importance, and every effort should be made to establish an early diagnosis.

Important Points: Persistency of occult blood in the stools and stomach contents, notwithstanding treatment (Elsener); extreme loss of appetite; anemia, gradually adopting the yellowish tinge of cachexia; marked stagnation without a palpable mass. Chemical findings of the acidity getting lower and having no tendency to increase with Riegel's test-meal (Gluczinsky) and, finally, absolute achylia, are positive clues. The Roentgen-ray, showing a defect in filling in certain portions of the stomach, speaks for carcinoma.

PROPHYLAXIS

In prophylaxis we must chiefly consider the class of cases we deal with, and as to what the symptoms present are due.

It is a well-known fact, particularly under American conditions, that many cases of hypersecretion and hyperacidity that gradually led to weakening of the stomach muscles and finally ulcer, are the out-

61. Aschoff and Friedenwald: On Frequency of Transmission of Ulcer of Stomach into Carcinoma, Boston Med. and Surg. Jour., May 29, 1913, No. 22, p. 796.

come of over-eating, hasty eating, and without any consideration as to quality. The people should be directed to partake of only two substantial meals daily; one in the morning, consisting of fruit, cereals, eggs, light coffee and bread and butter; only a light lunch at noontime, possibly buttermilk and biscuits; and the second chief meal at 6 o'clock (dinner) consisting of soups, plainly prepared fish and meats, fresh green vegetables, cooked fruits and light puddings. As a rule spicy foodstuffs, canned goods and foods of extreme temperature are to be avoided.

A class of persons who, as shown above, incline especially to ulcers is that of the status asthenicus, also having the stigmata of the disturbance in the vegetative nervous system. For these patients diet is of the utmost consideration. We must lay great stress on the essential importance of spare diet (Schonungs-diet) for some time. This consists of meats scraped or minced, vegetables strained, excluding such as have a tendency to gas formation (cabbage, etc.), only fruits which are cooked and strained; bread toasted, soups in the smallest possible quantities, served just as an appetizer; in general, little liquids, especially with meals; the fats of low melting point in sufficient quantities. We believe that in these cases the two-meal system ought also to be adhered to, in order to give the stomach a chance to empty itself. But it is of importance that such patients should rest from a half to one hour after meals, on the right side. Abdominal supports are also essential, and the toning up of the general system by hydrotherapeutics (mild morning douches), sponge baths, or a tempered half bath with cooler water poured over the back and frequent short vacations.

After a while we may start on a coarser diet (Uebungsdiet) or exercise diet, in which the foodstuffs are not so finely prepared.

In the majority of these cases the treatment outlined above will suffice without any medicinal aid.

Some patients, particularly those of the vagotonic type, with their contracted pupils, slow pulse, hypersecretion, moist skin, etc., should be given belladonna in some form.

In a third class of cases, in which the threatened symptoms are due to a chronic appendicitis, gall-bladder diseases, movable kidney or obstinate constipation, the underlying cause must be treated.

TREATMENT OF ULCUS VENTRICULI

Patients with ulcus ventriculi should, as soon as the diagnosis is established, be put to bed, to undergo a regular cure for ulcer.

Of late there has been inclination on the part of some to advocate the ambulatory treatment of ulcus ventriculi, and they claim equal success. We decidedly question whether many of the cases mentioned in literature

as being favorably influenced by the ambulatory method actually had ulcers.

Strauss and Bamberger even go so far as to have the patient undergo a regular cure for ulcer when only one or two symptoms, like hyperacidity or hypersecretion, are present. Such a radical course may be practicable under European conditions, where clinics and sanatoria are plentiful, and where there is ample provision even for the workingman to rest as long as necessary without losing his livelihood. In this country however, if repeated examinations show no occult blood, if the patient is fairly well nourished and modification of diet and medicinal treatment, to be outlined below, have a favorable influence, we may for three or four weeks try the ambulatory treatment. But if there be no decided improvement within a week, the patient should be put to bed.

Of what does the ambulatory treatment consist? We must insist on our patient adhering strictly to certain written rules, which are as follows: To restrict his work as much as possible for two or three weeks; to rest after his chief meals for one half to one hour, with warm applications to the epigastrium; to take his meals more frequently, and obey strictly as to quality and quantity, and to avoid all mental excitement and unnecessary bodily fatigue.

Diet: The first week, if there is marked pain, the patient is allowed, until pain subsides, luke-warm milk every three hours; daily quantity between 2½ and 3 liters. For patients who do not tolerate milk alone, we may add either some lime water to the milk, or, mornings and evenings when the patient is at home, add a fine cereal (hominy) to the milk. We can also increase the nutritive value of the milk by adding a half pint of sweet cream to the milk during the twenty-four hours.

Second Week—Morning: One or two soft boiled eggs, cereal, milk soup, one cup of milk. 10 a. m.: one cup of milk with cream, two zwieback and butter. Noon: one or two eggs, cereal, milk soup, one cup of milk. 4 p. m.: one cup of milk, two zwieback and butter. Evening: two eggs, cereal, milk soup, milk with cream, two zwieback and butter. 10 p. m.: one cup of milk.

Third week: Besides the foodstuffs mentioned in the first two weeks, the patient gets 60 gm. of scraped beef or minced veal, or scraped, cooked, unsalted ham, 50 gm. of mashed potatoes, or spinach or carrots in purée form, and toasted white bread.

Fourth week, we add cereal puddings made with butter, milk or cream (non-flavored), and at the end of this week apple sauce or baked apples.

Fifth week, we add to the list of meats, boiled chicken, chopped, sweetbreads or fish, and gradually increase the quantity of meat to 100 grams.

Medicinal, physical and hydrotherapeutic treatment will be discussed below.

TREATMENT OF THE ULCER WITH PATIENT IN BED

Since the time of von Leube, who gave the stomach the most complete rest of five, six and even seven days, in order to arrest peristalsis, diminish acidity and hypersecretion, the treatment of ulcer has changed. Lehnhart even took an extreme view in the other direction, claiming that it is just the starvation that prevents the healing of the ulcer; that because of the hyperacidity and hypersecretion we should supply enough proteins in a non-irritating and easily digestible form to bind the hyperacidity and hypersecretion.

To-day, as we try to base our treatment on the etiology and also to individualize, the treatment cannot be according to either extreme. The argument against von Leube's cure for ulcer, that starvation for the time outlined by him may prevent the healing of ulcer, is certainly not incorrect; on the other hand, Lehnhart's treatment is too radical, because of its tendency to increase stomach peristalsis at a time when rest is so essential for the stomach. The food also irritates the stomach mechanically, and according to Strauss it is liable to cause emboli.

Doubtless at the time when Lehnhart suggested his treatment the differential diagnosis between ulcus ventriculi and ulcus duodeni was not made with such certainty as to-day. The hyperacidity and hypersecretion associated with duodenal ulcer give rise to the so-called hunger pain, because the stomach empties itself quicker; hence in such ulcers, even in the first day of treatment, unless there is acute hemorrhage the Lehnhart course may be indicated.

The treatment that has proven useful to us is as follows: The patient is put to bed, in order to give body and mind complete rest. To give the stomach complete rest, also, no food is allowed by mouth for three or four days, during which rectal feeding is administered.

While the disadvantages of rectal feeding consist of the intestinal irritation that it is liable to produce, and the fact that so little of the food is absorbed that the patient is starved at best, we have on the other hand the advantage of relieving the patient's pain; and with the rectal feeding we introduce fluids into the system which quench the thirst and prevent the drying out of the tissues. These difficulties—the irritation and starvation—can be overcome, the former by adding tincture opii. in the dose of 15 or 20 drops to the nutritive enema, and the latter should be remedied by feeding the patient by the Murphy drop method, to be mentioned below.

METHOD OF RECTAL FEEDING

The first rectal feeding in the morning is preceded by a cleansing solution of normal saline, 1 pint. For some patients more than one cleansing enema a day will have to be given.

Experiments have established the fact that to a certain extent proteins, fats and carbohydrates can be absorbed by the colon, provided the ingredients be given in an absorbable form and be predigested with the corresponding ferments. The absorption of fat, which is the most refractory of these substances, is facilitated by the addition of pancreatin and sodium chlorid. With this object in view Friedman and Strauss[62] have advised the following cream enema:

Cream, 1 pint; pancreatin, 1 teaspoonful; pepton, 2 tablespoonfuls; grape sugar, 2 tablespoonfuls; salt, ½ teaspoonful. (Quantity for one enema.)

The next feeding may be the one advised by Boas:

Milk, one-half pint; 2 yolks of egg; 1 tablespoonful red wine (when there is no hyperchlorhydria); 1 tablespoonful Nestle's or Mellen's food.

Or, instead of this, Riegel's formula:

2-3 eggs; ½ teaspoonful salt; ½ pint peptonized milk.

Or Ewald's, consisting of

3 to 5 eggs; ½ pint 15 per cent. grape-sugar solution.

Outside of the first formula, advised by Friedman and Strauss, which we apply without change, we modify the Boas, Riegel and Ewald's formulae by using:

2 eggs; ½ pint peptonized milk; ½ teaspoonful salt; ½ pint 20 per cent. grape solution, administered slowly.

The grape sugar serves a double purpose, as it adds to the nutritive value by its carbohydrates, and aids markedly in absorption.

Alcohol we do not use in the enemas at all for two reasons, first, because by way of reflex it increases the secretion of the stomach, and second, because it irritates the intestines.

A very useful addition to the caloric value of rectal feeding is the introduction of nourishment per rectum by the Murphy drop method. We use 1 pint of peptonized milk and 1 pint of 20 per cent. grape-sugar solution. Such a feeding is given once a day, the formulas before mentioned twice daily.

If the patient is very thirsty he is allowed to rinse his mouth with cool water, and it is also essential to wash the teeth and mouth a few times daily to prevent parotitis.

On the fourth or fifth day we begin with 2 tablespoonfuls of cooled milk every hour, which amounts to about one-half liter daily. In addition to this the patient is given two rectal feedings—a cream feeding in the morning, and one-half pint of milk and one-half pint of 20 per cent. grape-sugar by the Murphy drop method about 4 p. m.

Just as soon as we find that the patient tolerates well the milk by mouth, we increase the quantity quickly, and on the sixth day we give him as much as 1 liter of milk in divided doses daily, and if his condition permits, we give him two soft boiled or raw eggs daily. If he can tolerate the two eggs and milk, we discontinue rectal feeding, and on the

62. Friedman and Strauss: Therap. d. Gegenwart, May, 1911.

seventh day we increase the milk to 1½ liters daily, and give four eggs daily.

Eighth day: 1½ liters milk and even 5 eggs; 35 gm. minced veal.
Ninth day: 1½ liters milk with cream; 5 eggs; 1 plate soup; 35 gm. scraped beef; 50 gm. minced veal.
Tenth day: 1½ liters milk and cream; 5 eggs; 1 plate soup; 35 gm. scraped beef; 50 gm. veal; 75 gm. cereal cooked in milk.
Eleventh day: 1 liter milk and cream; 5 eggs; soup; 35 gm. scraped beef; 50 gm. minced veal; 75 gm. cereals.
Twelfth day: 1 liter milk and cream; 3 eggs; soup; 50 gm. scraped beef; 50 gm. minced veal; 3 zwieback; 100 gm. cereal; 100 gm. potatoes mashed
Thirteenth day: 1¼ liters milk and cream; 2 eggs; soup; 50 gm. scraped beef; 50 gm. minced veal; 3 zwieback; 100 gm. potatoes; 100 gm. spinach purée.
Fourteenth day: 1½ liters milk and cream; 2 eggs; 300 cereal soup; 75 gm. beef scraped; 75 gm. veal minced; 5 zwieback; 100 gm. potatoes mashed; 100 gm. spinach purée.
Fifteenth day: 2,000 milk and cream; 4 eggs; soup; 75 gm. scraped beef; 75 gm. minced veal; 6 zwieback; 200 gm. potatoes purée; 100 gm. spinach purée; 50 gm. butter.

In the third week we gradually add toast, well prepared and strained cereals, a squab or fish, lamb chops, calves' brains or sweet breads. By the fourth week we include apple compote, baked apple and strained prunes.

The patient is allowed to leave his bed in the beginning of the third week for a short time during the day, and at the beginning of the fourth week he can remain up all day. While in bed a sponge bath twice daily, and light massage for the extremities ought to be given; also the application of hot flaxseed poultices twice daily for one or two hours, and a Priessnitz at night. The bowels should be kept open by enemas, preferably oil enemata to be retained over night.

MEDICINAL TREATMENT

One of the oldest remedies in the treatment of ulcus ventriculi is silver nitrate. J. Kauffman (New York) showed that silver nitrate exercises its benefit by increasing the mucus in the stomach, thereby protecting the stomach wall and neutralizing the secretion. This is an ingenious idea and has put the silver-nitrate treatment on a rational basis. It is prescribed in the following manner:

Argentinitratis, 0.2-0.3.
Aquae, 120.0.
Ft. solution, 1 tablespoonful.
Three times daily before meals in water.

We must remember, however, that silver nitrate does not agree with some people, because of its irritating property and the fact that it is liable to produce diarrhea and even argyria. It is, therefore, a two-edged sword, and not to be recommended unless other drugs have failed.

Another drug recommended is atropin. Atropin is used for its property of diminishing secretion, and thereby reducing the acidity; most important, however, is its antispasmodic property.

As outlined by von Bergman, atropin is particularly indicated in those patients who, in addition to the ulcer, show stigmata of vagotonia. With this we can wholly agree.

Atropin quite frequently relieves the pain, so that no other narcotics are needed. It is given either internally—0.0005-0.001, or subcutaneously in the same doses, or as belladonna extract 0.03 by suppository twice daily.

A drug more universally used than the above mentioned is bismuth subnitrate. This is an antacid, and also tends to cover the ulcerated mucosa, so serving as a protector. Bismuth is best given combined with magnesium oxid, in order to overcome the constipating effect.

Bismuth can be given in suspension with olive oil; it has then a more decided antacid and soothing effect.

Bismuthi subnitratis	20.0
Magnesia oxidi	10.0
Aequae	200.0

One tablespoonful three times daily one-half hour before meals in one-half tumbler of water.

A remedy which we consider of great usefulness in the treatment of ulcus ventriculi is olive oil, if the patient tolerates it. It is soothing, nourishing and also indirectly antacid, by the reflex action on the duodenum causing a flow of alkaline juice into the stomach; it has also an influence on the intestinal peristalsis. It should be given in ½ to 2 tablespoonfuls, three times a day, before meals.

P. Cohnheim administers oil with the yolk of an egg and 3 ounces of almond infusion. This infusion is made by putting forty sweet almonds and two bitter almonds into boiling water for a few minutes, removing the skins, then grinding the almonds in an almond grinder. Add one half pint of warm water, stirring constantly. Allow this mixture to stand for two hours, then strain through a cloth. It should be freshly prepared each day. If oil is not tolerated at all, sweet cream may be given instead, warm.

The alkaline treatment of L. Bourget[63] has proved very useful. Bourget reasoned that solution of bicarbonate of soda, when given on a full stomach, passes through the fold of Retzius directly to the pylorus, into the duodenum, from whence it regulates the opening of the pylorus, overcoming the spasm and causing a more rapid emptying of the stomach.

63. Bourget, L.: Krankheiten d. Magens., Wiesbaden, 1906.

This property of bicarbonate of soda solution indicates that the antacid effect of the drug does not lie in its concentration, but in its reflex action from the duodenum. We do not demand that bicarbonate of soda shall completely neutralize the acidity, because the quantity would have to be so large as to be really injurious. The solutions used by Bourget (1 per cent.) have a tendency to diminish the acidity only. By means of its above-named properties it not only overcomes the spasm at the pylorus, but also those in other parts of the stomach.

The 1 per cent. solution of sodium bicarbonate is administered not only at the height of acidity, but when the patient has pain or pyrosis. The solution is given regularly one to one and one-half hours after a light meal, and two to three hours after a heavy meal; besides that, at any time of the day or night when the patient is uncomfortable.

Mode of administration:

Sodii bicarbonatis purissimi	8.0-10.0
Sodii phosphatis sicci	4.0- 5.0
Sodii sulphatis sicci	2.0- 3.0

One powder in a quart of water taken ½-1 glass when necessary.

Or:

Sodii bicarbonatis purissimi	1.0
Sodii phosphatis sicci	0.4
Sodii sulphatis sicci	0.2

One powder in ½ glass warm water whenever necessary.

The treatment with alkalies can also be administered in the form of mineral water, preferably Karlsbad Muehlbrun, given warm, ½ pint on an empty stomach, and one hour before supper. This water does not agree with neurotic individuals, and a milder variety, like Celestin-Vichy, or Fachinger can be given instead.

Those alkaline waters which are very rich in gas should not be permitted, because of their property of distending the stomach and causing bleeding.

Francis W. Palfrey[64] used ox bile in fifty cases of ulcus ventriculi with good results. Although for a complete understanding of his reason for using bile we must refer to the original article, we will here give a short abstract.

It is physiologically a well-established fact (Cannon, Pawlow) that the chemical influence on the emptying of the stomach is exercised by the HCl on the gastric part, and the neutralizing power of the duodenum is brought about by the secretion of the duodenal mucosa, pancreatic juice and bile. A delay in emptying may as much depend on the failure of duodenum to neutralize the contents as on the disproportion in the acidity of the stomach. For this reason Palfrey gives ox bile in the dose

64. Palfrey, Francis W.: The Administration of Ox-bile in the Treatment of Hyperacidity and of Gastric and Duodenal Ulcer, Am. Jour. Med. Sc., June, 1913, clxv, 796.

of 0.25, three times a day, after meals, in order to stimulate the neutralizing power of the duodenum.

Glaessner[65] uses sodium glycocholate 0.2 with oil in capsules after meals, on the experimental basis that it neutralizes acidity.

The medicinal treatment outlined is also applicable to ambulatory cases. In these cases, when the autolavage property of the Carlsbad water in the morning does not suffice to give relief, we may wash the stomach out with alkaline water two or three times weekly for two or three weeks. We must be certain that there is no occult blood in the stomach or stools.

AFTER TREATMENT

The lasting effect and ultimate results of our treatment depend a great deal on continued observation of the patient. When discharged after five or six weeks, he should have a final thorough physical and chemical examination of the gastro-intestinal tract; and even when everything is found to be normal, the transition to a coarser diet (exercise diet) should be gradual. We gradually allow him boiled chicken, veal cutlets, lamb chops, steak well done and scrambled eggs; also different cooked fruits like peaches, prunes and pears in purée form. To the list of vegetables we add string beans, cauliflower and asparagus tips. Bread is allowed in a non-toasted form, but white, and one day old.

We dispense with all drugs, but advise an alkaline table water like Celestin or Fachinger; or, when expense is a factor, the above-mentioned 1 per cent. bicarbonate solution should be given in wine-glassful doses with meals.

Should the patient continue to show a tendency to hypersecretion, we should restrict salt to a minimum. Hydrotherapeutics in the form of a sponge bath or mild shower will prove useful. For those who can afford it, it is even advisable to take a month every year at a spa like Kissingen, Saratoga Springs or Karlsbad; or, if that is not possible, a home cure, consisting of taking mineral water one hour before breakfast and one hour before supper, should be maintained for a month.

TREATMENT OF HEMATEMESIS

Absolute rest in bed, flat on the back, foot of bed elevated, ice bag to the abdomen. In order to relieve the patient's anxiety, a small dose of morphin given hypodermatically (0.005 to 0.007) is useful. Light bandaging of the upper and lower extremities should be applied to obstruct the venous flow, but not to obliterate the pulse. Should the patient show considerable loss of blood we should try to replace the loss by rectal administration of Ringer's solution up to one pint, either by

65. Glaessner: Eine neue Therapie der Hyperacid, Wien. klin. Wchnschr., 1913, No. 39.

enema or by the Murphy drop method. If this alone is not sufficient, try hypodermoclysis of normal saline solution, or intravenous normal saline, to which 10 to 15 drops of 1:1,000 epinephrin (adrenalin) chlorid is added.

No further stimulation is, as a rule, necessary; in fact, the weak pulse is even advantageous, as it allows a coagulum to form. Should, however, the pulse be fluttering and rapid, more stimulation is indicated. The most useful means is camphor-oil, 10 per cent., 5 c.c.

Hemostatics: if we have nothing on hand, we at once resort to a sterilized 10 per cent. saline solution, of which 5 c.c. should be given intravenously. According to many authors, this has worked when everything else failed. Gelatin in sterilized tubes 20 c.c. intramuscularly is also efficient. Blood-serum (horse) is also hemostatic. Lavage of the stomach with ice-cold water to stop hemorrhage has been advised by Fleiner; by Ewald with hot water; by Bourget with liquor sesquichloridi solution (1 per cent.).

We personally have had no experience with lavage, and feel that in a great majority of cases we can get along without it. However, where blood-clots stay in the stomach as an irritant, and cause excessive vomiting, lavage would be the proper procedure; we must emphasize in that event the advisability of cocainizing the pharynx with a 2 per cent. solution, in order to prevent straining or gagging.

In hemorrhage we should not allow even rectal feeding for twenty-four to forty-eight hours. On the second day we may administer 10 per cent. grape sugar solution per rectum. The rectal feeding begins on the third day, and is kept up to at least the sixth day, taking good care of the mouth to prevent parotitis. The rest of the treatment is like that outlined above, only to be continued for a longer time to prevent recurrence.

It is universally agreed that hemorrhages should be treated internally. But should they show a tendency to repetition in the future, then operation is indicated during the interval.

TREATMENT OF COMPLICATED ULCER

Those ulcers which do not yield to the above outlined treatment are undoubtedly complicated. At present when, with the aid of the Roentgen ray, the penetrating of callous ulcer, persistent hour-glass contraction, and adhesion to different organs can be diagnosticated earlier, we should not fail to take advantage of such means, and when found the case should be turned over to the surgeon.

The degeneration of ulcer into carcinoma certainly does occur (Aschoff has it that carcinoma was the primary condition). It is, how-

ever, a clinical fact that, in patients in whom the symptoms have persisted for years, carcinoma has developed.

From a therapeutic standpoint it is essential to diagnose the condition as early as possible, in order to turn the case over to the surgeon. Here Elsener's[66] observation, that if occult blood persists notwithstanding treatment carcinoma should be suspected, is a most valuable one. That the perforating gastric ulcer belongs to the surgeon need hardly be mentioned.

In treatment of benign stenosis of the pylorus due to ulcer, it is gratifying to find that Kemp[67] has accomplished the task of following up his eighty-seven cases of motility disturbance of the stomach of various degrees, in which pyloric stenosis is included, and found that internal treatment has a decidedly better influence on motility than surgical interference. His views concur fully with our observations.

It should be remembered that even stagnation of twelve to twenty-four hours' duration is not due to the thickening of the ulcer, but to the associated pylorospasm; the mechanical obstruction of the food is also due to the over-loaded stomach wall, while the musculature is still in a condition to be able to propel the food.

In such cases, as in acute ulcer, mental and bodily rest is essential; thorough lavage of the stomach twice daily, morning and evening, with alkaline solutions; rectal feeding for days, gradually testing as to whether the stomach can still expel the liquids introduced. Milk, preferably peptonized, in small quantities, is the food to be started with.

Just as soon as we find that the morning lavage is clear of the food from the day before, we should then use the lavage once only, in the morning, and gradually increase the food in quality and quantity, similarly to ulcus ventriculi, with the exception that the food should be given in purée form for months. These patients should be made to understand their condition, in order to observe dietary rules and rest, and just as soon as they have the slightest sensation of fullness or regurgitation, to report at once. When there are signs of stagnation, lavage of the stomach should be instituted and diet modified accordingly, until conditions improve.

We advise surgical treatment only if a conscientious attempt, as outlined above, has no effect.

OPERATIONS AND RESULTS OF OPERATIONS ON ULCUS VENTRICULI

It is not within the domain of this article to discuss the question of the kind of operation which is most useful. The valuable contributions to this subject by the Mayos, A. A. Berg, John B. Deaver and others,

66. Elsener: Lehrbuch f. Ulcus Krankh., 1911.
67. Kemp.: Arch. f. Verdauungskr., 1913, No. 2.

throw a good light on the kind of operation most useful in individual cases.

We are considering the question chiefly from the internal standpoint, and we must always ask ourselves what are we to expect of the operation, and are the effects lasting? The symptoms of pain, hypersecretion, motility disturbances and occult blood, as pointed out above, when they do not yield to persistent internal treatment, demand surgical interference.

We know from experience that the symptoms that first and before all yield to surgical interference are the pain and bleeding. The next two most important symptoms, i. e., hypersecretion and disturbed motility, yield completely only in exceptional cases. In the majority of cases, as shown by Boas[68] and Kemp, the disturbance remains. This makes it imperative for us to observe the patient after the operation at certain intervals, to test the functions of the stomach, and to employ the Roentgen ray to see whether the new opening is acting. The Roentgen ray examination after an operation on an hour-glass stomach disclosed, in certain cases cited by Ewald, that the anastomosis did not include the upper part of stomach.

We must also bear in mind that patients suffering from ulcer of the stomach are predisposed to recurrences even after operation. Another complication arises through the fact that the acid gastric contents flow freely into the anastomosed intestine, causing occasional ulcus p. duodeni, or jejuni. The reason this is mentioned in detail is to show that the after-treatment must be kept up carefully.

68. Boas and Kemp: Berlin Gesellsch. f. Chir., 1913.

A SKIN REACTION INDICATIVE OF IMMUNITY AGAINST TYPHOID FEVER

*STUDIES IN TYPHOID IMMUNIZATION, III**

FREDERICK P. GAY, M.D., AND JOHN N. FORCE, M.D.
BERKELEY, CAL.

It is generally accepted that the prophylactic immunization of human beings with living or dead preparations of the typhoid bacillus protects to a marked degree against typhoid fever. This protection is particularly demonstrable in segregated bodies like armies where immunized and non-immunized men are subjected to even chances of infection. In spite, however, of the convincing evidence of this protection by vaccination in the aggregate, we have as yet little evidence on the actual duration of any method of immunization, and no certainty as to security of an immunized individual. Firth,[1] to be sure, on the basis of the scientifically assembled statistics from the British Army in India, has ventured the statement that anti-typhoid immunizations may be expected to protect absolutely for two and a half years, with further evidence that partial immunity is enjoyed for four or five years. It would aid enormously in estimating the duration of immunity in general, in determining the most efficient method of immunization, and particularly in ascertaining the individual protection, if some reaction indicative of more or less perfect immunity could be devised.

Certain of the antibody tests, particularly the agglutination reaction and the reaction of fixation, are of recognized value in the diagnosis of typhoid fever; they are, however, of no certain significance as measuring actual resistance to typhoid infection. We have simply to mention that a high agglutination reaction affords no assurance of protection against a relapse in the disease, and on the other hand, that it is well recognized that those who have recovered from typhoid fever soon fail to give the reaction in the majority of cases, although they are usually protected for life from a recurrence of the disease. Bloch and Creuze[2] found a sensitizer (fixation reaction) in the serum of individuals immunized with Chantemesse's vaccine which appeared in from five to seven days following the initial injection and persisted in all cases for

*From the Hearst Laboratory of Pathology and Bacteriology, and the Laboratory of Hygiene, University of California.

* Submitted for publication Nov. 13, 1913.

1. Firth: A Statistical Study of Anti-Enteric Inoculation, Jour. Royal Army Med. Corps, 1911, xvi, 589.

2. Bloch and Creuze: La sensibilisatrice dans le serum des subjets vaccinés contre la fièvre typhoïde, Compt. rend. Soc. de biol., 1912, lxxiii, 603.

at least four months; it was present in 83 per cent. of the treated patients for a year. They make no note of the presence of a similar antibody in recovered typhoids. Klien[3] has found the opsonic index of little value in indicating protection against typhoid fever. Moon[4] has obtained agglutinin reactions of varying intensity for at least a year after vigorous anti-typhoid immunization and appears justifiably sceptical as to their significance. Ardin-Delteil, Negre and Raynaud,[5] found the treatment of typhoid fever with vaccines increases the bactericidal power of the serum but not the agglutinins. Maverick[6] found a case that produced no agglutinins on repeated doses of vaccine.

The experimental results of Gay and Claypole on typhoid infection and immunization in rabbits, for the most part unpublished, show that the agglutination titer is of no value in measuring the *degree* of resistance to infection with the living organism. This is particularly true in immunization with sensitized cultures of typhoid bacilli, which give better protection but lower agglutinins than the untreated bacilli. This agrees in all details with the experimental and practical work with sensitized cultures in the hands of other investigators (Broughton-Alcock;[7] Ardin-Delteil, Negre and Raynaud;[8, 5] Garbat and Meyer[9]) who have uniformly obtained larger amounts of bactericidal substances but less agglutinins than when untreated cultures are employed.

It is evident, that the agglutination reaction, at least, is no measure of the grade or indeed of the existence of protection from typhoid infection. It may be that fixation or lytic tests would afford safer criteria, although they have the disadvantage of being more complicated.

SKIN REACTION

In our desire to find some method of indicating actual protection in human beings against typhoid fever, we have tried an adaptation of the v. Pirquet skin test with promising results.

---

3. Klien: The Opsonins in Typhoid Immunity. Bull. Johns Hopkins Hospital, 1907, xviii, 245.

4. Moon: Experimental Immunity in Relation to the Agglutination Reaction in Typhoid, Jour. Am. Med. Assn., 1913, lx, 1764.

5. Ardin-Delteil, Negre and Raynaud: Réchérches cliniques et expérimentales sur la vaccinotherapie de la fièvre typhoïde par le virus sensibilisé de Besredska, Ann. de l'Inst. Pasteur, 1913, xxvii, 644.

6. Maverick: Typhoid Vaccination and the Widal Reaction, Jour. Am. Med. Assn., 1912, lviii, 1672.

7. Broughton-Alcock: Vaccination for Typhoid by Living Sensibilized Typhoid Bacilli, Lancet, London, 1912, ii, 497.

8. Ardin-Delteil, Negre and Raynaud: Réchérches sur les reactions humorales des malades atteints de fièvre typhoïde traités par la vaccin de Besredka, Comp. rend. Soc. de biol., 1913, v, lxxiv, 371; *ibid.*, Sur la vaccinotherapie de la fièvre typhoïde, Compt. rend. Acad. Sc., 1912, clv, 1174.

9. Garbat and Meyer: Ueber Typhusheilserum, Ztschr. f. exper. Path., 1910, viii, 1.

The skin test has already been suggested as an additional method of diagnosis in typhoid fever, without, however, meeting with any general favor. Wolff-Eisner[10] could obtain no characteristic reaction in typhoid cases on intradermal inoculation of Ficker's Diagnosticum. Link[11] tried the skin reaction in nine cases with old concentrated bouillon cultures and obtained encouraging results in six of them. Most of these cases also showed a Widal reaction. Deehan[12] obtained a weak to moderate reaction in twelve cases of typhoid fever, whereas eight control cases showed none. Floyd and Barker[13] obtained positive results in nineteen out of thirty cases and none in eighteen controls, including two cases of paratyphoid infection. Chauffard and Troisier[14] find the reaction of little diagnostic value as it is also given, though in less degree, by control cases.

TECHNIC OF SKIN TEST EMPLOYED

The method of applying the typhoid skin test is a modification of the von Pirquet method of tuberculin testing as already introduced by one of us as a test for immunity against cow-pox vaccine.[15] It consists in producing an abrasion of uniform size and depth designed to cut just through the epidermis of the arm without drawing blood. This abrasion is produced by a complete twist of a chisel with straight edge (measuring 2.25 millimeters) and square corners supplied on specification by the Cutter Analytic Laboratory and so tempered as to resist sterilization by burning alcohol. The skin is prepared by cleansing with 95 per cent. alcohol. Various preparations of the typhoid bacillus have been tried with varying success, and the one actually chosen as the most efficient is prepared in a manner similar to the one employed in producing Koch's old tuberculin: 250 c.c. of 5 per cent. glycerin bouillon was inoculated with *B. typhosus* (Dorset Army Strain No. 5) and incubated for five days. It was then reduced without filtration to one-tenth of its original volume by evaporation over a 56 acetone bath for about eight hours. A control solution of sterile 5 per cent. glycerin bouillon was evaporated at the same time to equivalent volume.

Two uniform abrasions are produced on the upper arm or fore-arm of each patient tested, and the control solution gently rubbed into the inner spot with a sterile toothpick, and the "Typhoidin" solution similarly applied to the outer spot. The reactions are observed six and twenty-four hours later, and more rarely at subsequent periods. In a very few instances the six-hour period shows in positive cases an accelerated reaction which diminishes or actually disappears within twenty-four hours. Not infrequently, however, a positive test persists for a week. In the majority of cases the control spot shows a 2 mm. healed abrasion not surrounded by an areola; in the minority of cases a slight zone of traumatic

10. Wolff-Eisner: Die Opthalmo- und Cuti-diagnose der Tuberculose, Wurzburg, 1908.

11. Link: Ueber Hautreaktionen bei Impfungen mit abgetoteten Typhus, Paratyphosus B, and Koli-Kulturen, München. med. Wchnschr., 1908, lv, 730.

12. Deehan: The Typhoid Cutaneous Reaction, Univ. Penn. Med. Bull., 1909, xxii, 6.

13. Floyd and Barker: The Typhoid Cutaneous Reaction, Am. Jour. Med. Sc., 1909, xxxviii, 188.

14. Chauffard and Troisier: Réproduction expérimentale des taches rosées lenticulaires., Compt. rend. Soc. de biol., 1909, lxvi, 519.

15. Force: The Skin Reaction After Cow-Pox Vaccination: a Possible Aid in Public Health Administration, Cal. State Jour. Med., July, 1913; *ibid.*, A Test for Immunity Against Cow-Pox Vaccination. (In press.)

or irritative redness may occur about the abrasion. In these latter cases when there is a positive reaction in the "Typhoidin" spot there is no difficulty in noting and measuring the differences between its areola and the control redness. We have arbitrarily chosen a difference of 2.5 mm. between the two areolas as indicative of a positive reaction. The positive spot measures from 4 to 12 mm. in extreme diameter and is usually somewhat indurated and frequently clearly demarcated. In negative cases there is the same reaction or absence of reaction in the control and "Typhoidin" spots. In the routine examination, as a rule, twenty or more cases representative of the various categories were tested at a time, after history-taking, and to avoid prejudice, the nature of the reaction decided on before the history was referred to.

We have examined in all 124 cases by this method, repeating the test in a few cases where there was doubt in the result. We may consider first the results of the test in those cases that gave a satisfactorily detailed and designated history of typhoid fever as individuals in whom there is presumptive evidence of protection against typhoid fever.

TABLE 1.—CASES GIVING A DEFINITE HISTORY OF TYPHOID FEVER

No.	Patient	Interval Years	Skin Test	Remarks
98	W. H. S.....	41	Positive	
10	W. G. H.....	33	Positive	
117	J. G. O.....	20	Positive	
5	K.	14	Positive	
63	E. S.	10	Positive	
40	F. D.	10	Positive	
2	J. T. H.....	10	Positive	
1	T.	10	Positive	
30	M. C.	10	Positive	
28	T. C. B.....	9	Positive	
8	G.	8	Positive	
86	P. A. R.....	8	Positive	
29	T. D.	8	Positive	
17	M. K.	8	Positive	
20	R.	7	Positive	
13	A. L. H.....	7	Positive	
11	O. H.	6	Positive	
3	M. L. K.....	4	Positive	
4	F. J.	3	Positive	
126	J. T. F.....	16*	Negative ...	Suffering from neuritis.
33	D. G. M.....	4½*	Positive	Widal negative 1-25.

* Months.

As is seen from this table, twenty-one cases with a definite history ranging from 41 years to 4½ months previously were examined, and of these one only was negative. In other words, in the cases presumably protected against recurrence of typhoid fever, 95 per cent. gave a positive skin reaction.

We may tabulate at this point the results obtained in seven cases in which a history suggesting typhoid fever was obtained without report of a definite diagnosis to this effect. It may be remarked that in two

of these cases the history was obtained before the skin test was applied; in the other cases, the history was obtained by further inquiry in cases chosen as controls that showed an unexpectedly positive reaction (Table 2).

TABLE 2.—CASES WITH DOUBTFUL HISTORY OF TYPHOID FEVER

No.	Patient	Interval Years	Skin Test	Remarks
44	O. R. G.....	21	Positive	History of "malaria."
75	B. P. D.....	13	Positive	Severe intermittent; delirious; mother and sister affected.
45	H. H. S.....	12	Positive	Eight-day fever at 9 yrs.
96	A. P.	10	Positive	Intermittent fever over six weeks.
77	L. B. T.....	6	Positive	Ambulatory; delirium; 3 weeks; in tropics.
79	E. M.	1	Doubtful	"Malaria."
102	J. A. D.....	12	Positive	History of "malaria."

We may now consider the individuals tested as controls, from whom no history of an illness diagnosed as typhoid fever, or, on questioning, resembling typhoid fever, could be elicited. As the individuals who kindly volunteered for this test were for the most part medical students, an intelligent cooperation in history taking has been assured.

TABLE 3.—CASES WITH NO HISTORY OF TYPHOID FEVER (CONTROLS)

No.	Name	Reaction	No.	Name	Reaction
32	H. A. T....	Negative.	50	R. S. B.	Negative
14	Mrs S.	Negative.	53	H. P. H.....	Negative
22	O. A. S....	Positive	16	B.	Negative
6	B.	Negative	78	S.	Negative
7	S.	Negative	80	R. H. H. ...	Negative
9	W. G. S....	Negative	83	P. F. A.....	Negative
73	F. G. L....	Negative	84	Mrs. R.....	Negative
72	J. A. O....	Negative	82	A. S.	Doubtful
71	H. A. F....	Negative	88	W. C. F. ...	Doubtful
70	W. E. C....	Negative	94	H. H. M....	Negative
69	L. M. N....	Positive	92	D. R. M. ...	Negative
67	R. R. N....	Negative	103	M. L. C.....	Negative
66	C. L.	Negative	108	E. R.....	Negative
64	L. M. B....	Negative	107	O. M.....	Negative
58	F. P.	Positive	109	Z. Y. K.....	Negative
35	R. S. A....	Positive	101	J. E. H. ...	Negative
37	W. C. S....	Negative	97	E. H.	Negative
74	D. C.	Negative	95	L. L. C.....	Negative
46	J. A. J....	Negative	100	D. S.....	Negative
47	E. C.	Negative	110	L. W.....	Negative
49	E. W. S....	Negative			

As is evident from the table, of the forty-one negative control cases tested, thirty-five or 85 per cent., gave a negative "Typhoidin" reaction, two were marked as doubtful, and four only, or 9 per cent., were distinctly positive. In view of the contrast between these cases and those with a positive typhoid history, and the apparent relative reliability of the reaction in the positive cases, the question naturally arises as to the possibility of a mild or abortive attack of typhoid fever in the 9 per cent. of reactors with a negative history.

Our results to this point would seem to establish beyond doubt the value of our cutaneous test as differentiating with a high degree of accuracy between those who have had typhoid fever and those who have not. But as has already been mentioned, our principal interest in devising this test has been its use as an indicator of protection in those who

TABLE 4.—PATIENTS VACCINATED AGAINST TYPHOID (ARMY METHOD)

No.	Name	Interval Years	Reaction
135	A. D. P.....	4½	Positive.
111	J. I. M.....	4¾	Positive.
113	M. F. D.....	3	Positive.
127	J. W.	2	Negative.
130	F. A. S.....	2	Negative.
120	S. G.	2	Negative.
132	L.	2	Positive.
134	L. L. B.....	1¾	Positive.
123	A. F. W.....	1½	Negative.
125	W. J. F.....	1½	Negative.
129	A. C. W.....	1—2*	Negative.
116	L. L. F.....	11½*	Positive.
119	J. P. K.....	11*	Positive.
133	F. C.	9	Positive.
118	R. A. G.....	8*	Positive.

* Months.

have been artificially immunized against typhoid fever. Inasmuch as it does occur in recently vaccinated individuals, we trust it may eventually be relied on as truly indicating protection, may be used to test the relative immunizing values of different vaccine preparations, and may be currently employed in vaccinated individuals to mark the period when re-vaccination should be recommended.

Our tests in immunized individuals are assembled in Tables 4, 5 and 6, which are segregated in accordance with the method of vaccination employed, and arranged in accordance with the intervals that had elapsed between vaccination and the test.

The Army method consists, as is well known, in the inoculation of three doses of a killed culture of a mild and long cultured strain of *B. typhosus*, given at intervals of a week or ten days. The doses are

TABLE 5.—PATIENTS VACCINATED WITH CUTTER VACCINE

No.	Name	Interval Years	Reaction
34	G. F. R.....	4	Positive.
19	F. L. K.....	15*	Positive.
140	H.	1	Positive.
141	K.	1	Negative.
142	S.	1	Positive.
143	Dr. S.	1	Positive.

* Months.

TABLE 6.—PATIENTS VACCINATED AGAINST TYPHOID WITH SENSITIZED VACCINE (METHOD OF GAY AND CLAYPOLE)

No.	Name	Interval Months	Reaction
31	L. R. B.....	8	Positive.
25	E. J. C.....	8	Positive.
24	J. N. F.....	8	Positive.
23	F. P. G.....	8	Positive.
21	E. S. B.....	8	Positive.
34	F. C. C.....	8	Positive.
26	G. Y. R.....	7	Positive.
18	A. F.	7	Positive.
91	E. W. F.....	7	Positive.
81	J. M.	6	Positive.
85	O. S. C.....	6	Positive
39	W. D. H.....	6	Positive
41	M. G. W.....	6	Positive
38	D. H. H.	6	Positive
43	L. W. B.....	6	Positive
42	K. P. F.....	6	Positive
54	W. A. B.....	6	Positive.
61	C. D. H.....	5	Positive.
51	M. S.	5	Positive.
48	M. A.	5	Positive.
52	W. H.	5	Positive.
68	W. G. R.....	4	Positive.
27	G. L. G.....	3	Positive.
76	R. P.	3	Positive.
15	W. A. S.....	1	Positive.
105	E. S.	3*	Positive.
106	E. W.	3*	Negative.
90	S.	3*	Positive.
93	E. R. Z.....	2*	Positive.
99	F.	2*	Positive.
104	J. S.	2*	Positive.
87	F. G.	10†	Negative‡
89	M. B.	10†	Positive§
56	E. F. M.....	1*	Negative¶

* Weeks. † Days. ‡ Widal positive 1-50. § Widal doubtful 1-50. ¶ Widal negative 1-25.

usually 250, 500, and 500 millions of bacteria. The reaction produced is now reported to be mild. Immunization with the Cutter vaccine is similar to the Army method, but from evidence that has come to us the marked or severe reactions are not inconsiderable in number.

The vaccine at present furnished by Gay and Claypole has been utilized in vaccinating over 900 individuals, for the most part University students, and its freedom from untoward effects has been reported by Force.[16] The full report of the method of preparation and the experimental study by which the superiority of this vaccine over the ordinary vaccine is evidenced, will soon be published in sequence to a series of studies that is now appearing in this journal.[17] It will suffice at this point to state that it is a preparation of sensitized (Besredka) typhoid bacilli precipitated and sterilized by alcohol, ground in an agate mortar, weighed, and suspended in 0.5 per cent. carbolated saline solution. Three injections of 1/16 mg. (= 500,000,000 bacteria) are given at *two- or three-day* intervals. A further perfectioning of the method from the standpoint of reactions and immunizing value is in progress.

A study of these tables shows that of tweny-one individuals in the army and in civil life vaccinated with killed cultures of typhoid bacilli (Army or Cutter vaccine) at intervals of from eight months to four and three-quarter years previously, fourteen gave a positive skin reaction. All the cases vaccinated by the Gay-Claypole vaccine at from one to eight months previously gave positive reactions (25 cases). Of nine cases vaccinated three weeks or less previously, three did not react. In the later cases immunity doubtless was not fully established. Owing to the differences in point of time elapsed, no comparisons of the relative efficiency of the two methods can be made or is intended.

Agglutination tests (Widal) have been noted in a few instances. A complete comparison between the Widal test and the skin reaction in a large number of cases would be of interest, although the unreliability of the agglutination titer as indicative of immunity has been already noted. This is particularly true in the case of employment of sensitized vaccines, although the latter method gives indications of perfect immunity up to eight months, as judged by the skin test.

Obviously, it is too early to refer to the skin test as of more than presumptive value in indicating typhoid immunity. An extended series of observations over a long period of time checked by morbidity statistics in large bodies of individuals is necessary before we can assume that the test is of certain prognostic significance. As a working basis, however, we feel justified in recommending re-vaccination in individuals

16. Force: Institutional Vaccination Against Typhoid Fever, Am. Jour. Pub. Health, 1913, iii, 750.

17. Gay and Claypole: THE ARCHIVES INT. MED., xiii, No. 1.

who at any time subsequent to a month after vaccination fail to give a positive skin reaction.

We wish to thank Lieutenant-Colonel E. B. Frick, Major Roger Brooke, and Captain W. B. Snow of the Medical Corps, United States Army, stationed at the Lettermann General Hospital, for allowing us to examine and report on soldiers under their care who had been vaccinated previously by the army method.

CONCLUSIONS

A preparation of the typhoid bacillus ("Typhoidin") in all respects similar to Koch's old tuberculin produces a clear-cut cutaneous reaction by the von Pirquet method in 95 per cent. of cases that have recovered from typhoid fever (20 cases positive out of 21). Two of the cases had suffered from the disease forty-one and thirty-three years before, respectively. The reaction is negative in 95 per cent. of individuals without history of typhoid fever (41 cases tested). The 9 per cent. of these supposedly control individuals that gave a distinct positive reaction may be suspected of having had a mild and undiagnosed attack of typhoid fever. Of fifteen individuals vaccinated by the Army method from four and three-quarter years to eight months previously, nine gave a positive skin reaction. Twenty-five individuals vaccinated by the Gay-Claypole sensitized vaccine for from one to eight months previously gave uniformly a positive reaction.

No comparison is intended in the efficacy of the two methods, although it is suggested that the skin test may eventually be used for such a determination. It is further suggested that the test is of presumptive value in indicating protection against typhoid fever whether acquired by recovery from the disease or by artificial immunization against the disease. The test may eventually be used as an indication for re-vaccination in the individual case.

THE INFLUENCE OF LITHIUM AND ATOPHAN ON THE URIC ACID EXCRETION OF A GOUTY PATIENT*

AMY L. DANIELS
COLUMBIA, MO.

Recent work of Folin and Lyman[1] points to the conclusion that gout is caused by an accumulation of uric acid in the blood with a subsequent deposition of this in an insoluble form in the various tissues of the body, particularly in the joints and synovial membranes. The retention and consequent accumulation is due to a deficient and restricted power of the kidneys. By means of the new colorimetric method of Folin and Denis[2] these investigators have analyzed the blood from a large number of patients suffering from gout and have found the uric acid content higher than in normal individuals; in these patients the blood was frequently found to have reached the saturation point for this compound, namely, 4 mg. in 100 c.c. of blood. Atophan (2-phenylquinolin-4-carbonic acid) caused a decrease in the amount of uric acid in the blood and a corresponding increase in the uric acid eliminated. Nicolaier and Dohrn,[3] Plehn[4] and Haskins[5] have shown that this increase is followed by a sudden decrease, and for some days the output is less than during the period preceding the administration of the atophan. The conclusion is that atophan removes the uric acid from the blood by increasing the secreting power of the kidneys, but it does not mobilize the deposited urates.

In view of these results of Folin and Lyman the problem of finding a solvent for the uric acid in the blood of gouty patients no longer interests us. In whatever form this exists it can be removed by stimulating the kidney functions. We may speculate on a future when there shall be no more gout; a periodic dose of atophan will remove the accumulated uric acid and thus prevent the deposits which are now a conspicuous feature of this disease. But the problem of removing these deposited urates, of helping those who are now suffering, as well as of determining wherein the kidneys fail in fulfilling their normal functions, remains unsolved.

---

*From the Department of Home Economics, University of Missouri.
*Submitted for publication Nov. 24, 1913.

1. Folin and Lyman: Jour. Pharm. and Exper. Therap., 1913, iv, 539.
2. Folin and Denis: Jour. Biol. Chem., 1913, xiii, 469.
3. Nicolaier and Dohrn: Deutsch. Arch. f. klin. Med., 1908, xciii, 331.
4. Plehn: Deutsche. Med. Wchschr., 1912, No. 3.
5. Haskins: Jour. Pharm. and Exper. Therap., 1913, v, 63.

Formerly solutions of lithium salts constituted one of the most used remedies for gout and rheumatism. The rationale of this treatment was based on some early work of Ure,[6] who found that uric acid is much more soluble in solutions of lithium salts than in the corresponding salts of potassium and sodium. The assumption was that lithium introduced into the organism dissolved the uric acid and made it more easily excreted. Later work showed that the reaction which took place so readily in the test-tube when lithium and uric acid were the only reacting substances did not occur when salts of phosphoric acid, in similar concentration to those in the blood, were present; instead, the lithium formed an insoluble compound with the sodium phosphate. Lithium as a remedy for gout fell into disrepute.

There is a paucity of data in the literature relative to the effect of lithium on the uric acid elimination. All the evidence which I have been able to find pertaining to the therapeutic effect of lithium in gout has been the result of test-tube experimentation. It is conceivable that those changes which take place in the test-tube do not occur when the lithium is introduced into the body. In the blood-serum the salts are dissociated into their ions, and we have to deal only with sodium, calcium and potassium ions and with uric, chloric, carbonic, phosphate and sulphate ions existing side by side. We have no evidence that lithium in the body will form insoluble compounds with any of the ions present. Furthermore, a solution of lithium citrate when added to filtered pig's blood causes no precipitation of the inorganic constituents.

The tophi of the joints are made up largely of sodium and potassium urates with a small proportion of calcium urate. The problem, then, of removing these from the body is getting the sodium, potassium and calcium urates into solution. Because of the low atomic weight of lithium, a comparatively small amount is required to produce a given reaction. This, then, would seem the ideal cation to introduce into the body to bring about the desired solution. Experiments[7] have been reported in which cartilage impregnated with sodium urate has been suspended in aqueous solutions of the carbonates of lithium, potassium and sodium; at the end of forty-eight hours the cartilage suspended in the lithium solution was restored to its normal condition, the cartilage in the potassium solution was much acted on, while that in the sodium was unaffected. Luff[8] aimed to determine the solubility of sodium biurate in artificial blood-serum to which he added different proportions of lithium carbonate and lithium citrate, as well as other inorganic salts. The artificial blood-serum consisted of 0.5 gm. of sodium chlorid, 0.2

6. Ure: Med. Times, 1844, xi, 145.
7. Garrod: Quoted from Luff: Gout, p. 181, 1899.
8. Luff: Gout, p. 183, 1899.

gm. of sodium bicarbonate and 100 c.c. of distilled water; this, Luff maintained, represented the blood-serum so far as the saline ingredients are concerned. Neither of the lithium salts increased the solubility of the solution for sodium biurate. But the conditions in neither group of experiments were comparable with those existing in the body. It is not possible to surround the tophi with a medium consisting only of lithium salts; nor is the blood-serum such a simple mixture as Luff's artificial serum would indicate. In the latter experiments the failure of the sodium urate to go into solution has been attributed to the preponderance of the sodium ions in the serum. While it is true that any two salts susceptible of dissociation, which contain an electric ion in common, mutually diminish each other's solubility, the converse of this proportion has been found to be true, and salts possessing no electric ion in common may mutually increase each other's solubility in a fluid. The ever-changing ionic environment surrounding the urate deposits in the body was not duplicated in Luff's experiments. It is not improbable that the deposited urates may be slowly dissolved by the introduction of lithium ions.

If, in the past, substances capable of causing a solution of the deposited urates had been introduced into the gouty body, the evidence of such a solution would not have been forthcoming, for in this disorder it has been shown that the blood is already saturated with uric acid and the kidneys are unable to relieve the condition. Since we now have a substance which makes the kidneys more permeable to uric acid, it seemed advisable to determine if lithium has any influence on the urate deposits in those suffering from gout. It was in order to test this point that the investigation here reported was undertaken.

The patient, a woman of 55, has been a sufferer from chronic gout for at least ten years. The disease is apparently well advanced, for the joints of the fingers, toes and knees show marked deposits. Throughout the investigation the patient was kept on a liberal but purin-free diet. The uric acid elimination was taken as the criterion of the solution of deposited urates. The uric acid analyses were made according to the method of Folin and Denis.[2]

The accompanying table gives the data of the investigation.

It will be noted that the uric acid elimination (0.26 gm.) during the preliminary period, that is, before any atophan was taken, was somewhat lower than that of normal individuals, which according to Magnus-Levy[9] is from 0.3 to 0.6 gm. in twenty-four hours. Atophan caused an increase of 72 per cent. in the first excretion. Following the atophan (Period 3) the output was slightly lower than that of the former period. These results are comparable with those of other investigators and have

9. Magnus-Levy: Am. Jour. Med. Sc., 1910, cxl, 625.

been explained on the theory that the atophan caused a depletion of the uric acid of the blood. The introduction of 15 gr. of lithium citrate (5 grains three times a day) during a time when no atophan was being given did not influence the uric acid output (Period 4). Atophan (Period 5) was again given, together with lithium. The average output

EXCRETION OF URIC ACID AS INFLUENCED BY ATOPHAN AND LITHIUM CITRATE

Period	Date	Urine Volume c.c.	Uric Acid Gm.	Atophan Gm.	Lithium Citrate Grains	Uric Acid Average Gm.
	7/14	1,545	0.262	.....	.....	
1	7/15	960	0.297	.....	.....	0.26
	7/16	1,600	0.232	.....	.....	
2	7/18	2,255	0.491	3 × 1.5*	.....	0.455
	7/19	2,120	0.410	3 × 1.5	.....	
	7/20	1,635	0.245	1 × 0.5	.....	
3	7/21	1,440	0.243	.....	.....	0.242
	7/22	1,445	0.238	.....	.....	
	7/24	1,615	0.189	.....	3 × 5†	
4	7/25	1,515	0.313	.....	3 × 5	0.244
	7/26	1,935	0.255	.....	3 × 5	
	7/28	1,660	0.22	.....	3 × 5	
	7/29	1,796	0.38	3 × 0.5	3 × 5	
5	7/30	2,245	0.345	3 × 0.5	3 × 5	0.311
	7/31	1,490	0.257	3 × 0.5	3 × 5	
	8/1	2,580	0.304	3 × 0.5	3 × 5	
	8/2	2,005	0.282	3 × 0.5	3 × 5	
6	8/3	1,380	0.270	3 × 0.5	.....	0.27
	8/4	1,395	0.269	3 × 0.5	.....	
	8/5	1,915	0.381	3 × 0.5	6 × 5	
7	8/6	2,325	0.453	3 × 0.5	5 × 5	
	8/7	2,365	0.386	3 × 0.5	4 × 5	0.42
	8/8	2,175	0.439	3 × 0.5	5 × 5	
	8/9	2,180	0.431	3 × 0.5	5 × 5	
	8/16	....	....	3 × 0.5	4 × 5	
8	8/17	....	....	3 × 0.5	4 × 5	
	8/18	1,190	0.370	3 × 0.5	4 × 5	0.37

* One and one-half grams three times a day.
† Five grains three times a day.

for five days was 27 per cent. higher than during the time (Period 4) when no atophan was being given. This increase, we may assume, was due to the endogenous uric acid which had piled up in the blood since the former dose of atophan, eight days previous. During Period 6 the atophan was continued but the lithium was discontinued; there was a slight decrease in the elimination—from 0.31 gm. to 0.27 gm.; but as

this period lasted only two days I attach no significance to the slight drop. During the following five days (Period 7) more frequent doses of lithium (from 20 to 30 grains a day) together with atophan were given. The increase in the elimination—55 per cent.—was unmistakable; it very nearly equaled the output during the first atophan period when the blood was presumably saturated with uric acid. After a week of rest, while the patient was still on a purin-free diet, another trial was made. As in the previous tests atophan and the more frequent doses of lithium were given. Only one analysis was made, on the third day. The output, 0.37 gm., compares with that of the preceding period. The smaller quantity of lithium apparently had very little, if any, influence on the uric acid elimination, but the larger amount caused such an increase as to lead us to believe that the blood had again become saturated with uric acid.

In the absence of another reasonable explanation, the increase in the uric acid elimination when both atophan and lithium were being taken must be attributed to a solution of some of the deposited urates. The output at this time corresponds to the excretion after the first dose of atophan when the blood was presumably saturated. The fact that atophan had been given for seven successive days before the larger quantity of lithium would preclude the possibility that the blood had again become saturated with endogenous uric acid. But conclusions should not be drawn from a single series of tests with one patient.

It is impossible to continue this research for some time at least. Therefore these data are reported with the hope that they will stimulate further investigation of this subject.

COMPARATIVE STUDY OF PHENOLSULPHONEPHTHALEIN ELIMINATION AND THE INCOAGULABLE NITROGEN OF THE BLOOD IN CARDIORENAL DISEASES *

J. HOWARD AGNEW, M.D.
ANN ARBOR, MICH.

INTRODUCTION

Since its introduction by Rowntree and Geraghty,[1] the phenolsulphonephthalein test has to a great extent superseded all other tests of this class as an index of renal efficiency. The excretory ability of the kidney is measured by injecting a definite foreign substance and noting the amount eliminated within a definite time. Since Provost and Dumas[2] found large quantities of urea in the blood of nephrectomized dogs, and since Babington working with Bright[3] noted the large amount of urea in the blood of a nephritic, however, attention has been directed to the incoagulable nitrogen of the blood with the idea that its determination would indicate the permeability of the kidney to normal or abnormal nitrogenous metabolic products.

A large number of observers[4] have studied the urea of the blood and have noted a decided increase in patients with uremia, eclampsia, acute mercury poisoning and cholera.

Strauss[5] was the first to study systematically the blood in nephritis. He collected a large amount of data and found that in nephritis there was generally an increase of the incoagulable nitrogen, which he regarded as an evidence of renal insufficiency.

Owing to the variety of methods of precipitating the proteins and particularly of determining the urea nitrogen, markedly varying results have been obtained by various authors. Recently Folin and Denis[6] have devised a colorimetric method for estimating urea and nitrogen which requires but little blood, and in their hands has been very accurate. We have used this method in the present study.

---

* From the Department of Internal Medicine, University of Michigan.
* Submitted for publication Sept. 31, 1913.

1. Rowntree and Geraghty: Jour. Pharm. and Exper. Therap., 1910, i, 579.
2. Prevost and Dumas: Quoted by Schöndorff, Arch. f. d. ges. Physiol., Pfluger's, 1899, lxxiv, 307.
3. Bright, R.: Guy's Hosp. Rep., 1836, i, 360.
4. For an historical summary of this work with references, see Schöndorff: Arch. f. d. ges. Physiol., Pfluger's, 1899, lxxiv, 307.
5. Strauss, H.: Die chronische Nierentzündungen in ihrer Einwirkung auf die Blutflüssigkeit und deren Behandlung, Berlin, A. Hirschwald, 1902.
6. Folin, O., and Denis, W.: Jour. Biol. Chem., 1911, xi, 527.

The French, headed by Widal, Javal and Ambard, have used the hypobromite method to determine the "urea," as they term it, in the blood, and from these determinations on a large number of patients they have drawn very definite conclusions, especially in regard to the prognostic significance of increased amounts of urea in the blood. While this method is chemically imperfect, yet because of its extensive use by the French, we have used it in conjunction with the determinations by Folin's method.

The objects of the present study were to determine what relation, if any, existed between phthalein excretion and the incoagulable nitrogen of the blood; whether the relation of urea nitrogen to total nitrogen was of any significance; to what extent the hypobromite method could be depended on; and what diagnostic or prognostic value may be attributed to an increase in the incoagulable nitrogen of the blood.

METHODS

The phthalein test was done by intramuscular injection according to the original technic of Rowntree and Geraghty,[1] and the values given are percentages of excretion over a two-hour period.

The determination of urea nitrogen and the total incoagulable nitrogen, according to the method of Folin and Denis,[6] was briefly as follows:

Blood was obtained from the median basilic vein by puncture and allowed to flow into a vessel containing a little powdered potassium oxalate to prevent coagulation. The blood was precipitated with chemically pure, acetone-free methyl alcohol and the filtrate reprecipitated with an alcoholic solution of zinc chlorid. Samples of this second filtrate were taken for analysis. For the nitrogen determination the alcohol was evaporated and the residue decomposed by heating with sulphuric acid and potassium sulphate, a miniature Kjeldahl. This was then made strongly alkaline and the ammonia aspirated by an air-current into a dilute solution of hydrochloric acid which was Nesslerized, and the amount of nitrogen estimated by comparison in a Doboscq colorimeter with the color of a Nesslerized standard solution of ammonium sulphate. For the urea determination the alcohol was evaporated by aspirating an air-current through it and the urea hydrolyzed by heating with acetic acid and potassium acetate at a temperature of 155 C. (311 F.). After hydrolysis the solution was made alkaline, the ammonia aspirated and the nitrogen estimated as above. This portion also contains the preformed ammonia of the blood and is designated as the urea-ammonia fraction. Separate determinations of ammonia were not made, nor has any account been taken of other non-precipitable nitrogenous bodies in the blood.

The advantages of Folin's method are its accuracy and delicacy and the fact that but little blood is needed. The disadvantages from a clin-

ical standpoint are that it is technical, time-consuming and requires considerable care and experience before accurate results can be obtained. All analyses were made in duplicate and the determinations were not regarded as satisfactory unless the colorimetric readings checked within 5 per cent. Farr and Austin[7] have experienced difficulty in obtaining concordant results in the urea determination, and we have also had this trouble, it often being necessary to run five or six samples before getting a check. We have no explanation to offer for this difficulty, but because of it we have less confidence in our figures for the urea-ammonia nitrogen than in those for total incoagulable nitrogen. In the table the results obtained are expressed as incoagulable nitrogen per 100 c.c. of blood, urea-ammonia nitrogen per 100 c.c. of blood, and from these figures is computed the urea[8] per 100 c.c. of blood and the percentage relation of urea-ammonia nitrogen to total incoagulable nitrogen.

For the determination of nitrogen by hyprobromite, a slight modification of the method used by Widal[9] was employed, and in conformity with the French workers the values obtained are expressed as urea per 100 c.c. of blood. The method was as follows:

Blood was obtained as for the Folin method, and of this 10 c.c. were added, drop by drop, to 115 c.c. of chemically pure, acetone-free methyl alcohol, stirred well and filtered through a dry filter. The filtrate at this point was not treated with zinc chlorid as in the Folin method, and this may account for some variations in results which will be mentioned later. One hundred c.c. of the alcoholic filtrate (corresponding to 8 c.c. of blood) was then evaporated at a low temperature on the water-bath almost to dryness. The residue was taken up with a few cubic centimeters of distilled water, washed carefully into a ureometer tube of the Yvon type, decomposed with sodium hypobromite, the volume of liberated nitrogen determined with regard to temperature and the equalization of pressure, and the amount of urea calculated from the volume of nitrogen found. Owing to the amount of blood required in this estimation, duplicate analyses could be made in only a few instances, and therefore the results could not be checked. The advantages of the hypobromite method are that it is simple and can be quickly done. The analyses by the two methods were made on blood taken at the same time.

7. Farr, C. B., and Austin, J. H.: Proc. Soc. Exper. Biol. and Med., 1913, x, 169.

8. Since the ammonia nitrogen of the urea-ammonia fraction is an unknown variable the amount of urea computed from these figures is somewhat in excess of the actual amount.

9. Widal, F.: Le mouvement medical, 1913, i, 1.

NORMAL VALUES

The normal phthalein elimination in two hours is generally given at from 60 to 85 per cent. of the amount injected, with the first figure as the lower limit.

When we come to consider the amount of incoagulable and urea nitrogen normally in the blood, we are confronted by a great variety of figures, depending on the way in which the proteins of the blood were precipitated and the methods which were used for the urea determination. Schöndorff,[10] who precipitated the proteins with phosphotungstic acid and determined the urea by the method devised by him, gives 61 mg. per 100 c.c. of blood as the normal urea content. Strauss[8] precipitated with acetic acid and found 20 to 35 mg. incoagulable nitrogen per 100 c.c. of blood as normal, of which 50 to 75 per cent. was urea nitrogen. Von Jaksch,[11] who precipitated with phosphotungstic acid, found the urea nitrogen to be 23 to 28 mg. per 100 c.c. of blood. Obermayer and Popper,[12] after removing the proteins with acetic acid, found the normal incoagulable nitrogen to be 36 mg. per 100 c.c. of blood, and, after fractionating with tannic and phosphotungstic acids, found the urea nitrogen to be 18 mg. per 100 c.c. of blood. Hohlweg[13] precipitated with acetic acid and monocalcium phosphate and found the normal incoagulable nitrogen per 100 c.c. of blood to be 51 mg., of which 31 mg. was urea nitrogen. Foster[14] removed the proteins by precipitation with alcohol and found the incoagulable nitrogen per 100 c.c. of blood in non-nephritics to vary from 33 to 54 mg., of which the urea nitrogen was 20 to 39 mg.; Strauss,[15] in a more recent publication, precipitated the proteins according to Folin and Denis, and gives 30 to 40 mg. per 100 c.c. of blood as the normal amount of incoagulable nitrogen. Folin and Denis,[16] using their own method, give the incoagulable nitrogen per 100 c.c. of blood at from 22 to 26 mg., of which 50 per cent. is urea nitrogen. Oszacki[17] precipitated with uranyl acetate and gives 42 mg. per 100 c.c. of blood as the normal amount of incoagulable nitrogen, of which 50 per cent. is urea nitrogen. While Farr and Austin,[7] using Folin's method, found that patients showing no evidence of kidney insufficiency, showed a variation in incoagulable nitrogen of 16 to 43 mg. per 100 c.c. of blood, of which 50 to 60 per cent. was in the urea-ammonia fraction. Folin and Denis[16] also emphasize the fact that as soon as any other than

10. Schöndorff: Arch. f. d. ges. Physiol., Pflüger's, 1899, lxxiv, 358.
11. Von Jaksch: Quoted by Hohlweg: Deutsch. Arch. f. klin. Med., 1912, civ, 216.
12. Obermayer and Popper: Ztschr. f. klin. Med., 1911, lxxii, 332.
13. Hohlweg: Deutsch. Arch. f. klin. Med., 1912, civ, 216.
14. Foster, N. B.: THE ARCHIVES INT. MED., 1912, x, 414.
15. Strauss, H.: Ztschr. f. Urol., 1913, vii, 287.
16. Folin, C., and Denis, W.: Jour. Biol. Chem., 1913, xiv, 29.
17. Oszacki: Ztschr. f. klin. Med., 1913, lxxvii, 1.

perfectly healthy persons are considered, or when any sort of clinical material is taken, higher values are obtained, even though there are no evidences of renal disease.

In dealing with the amount of incoagulable nitrogen in the blood, there are several factors to be considered, among which are the diet of the patient and the time of day at which the specimen of blood is taken. Widal and Lemierre[18] and Hohlweg[18] have shown, respectively, how the amount of protein ingested and how the length of time after a meal influences the incoagulable nitrogen content of the blood. Practically all of the cases studied by us have been on a low protein diet, containing from 50 to 75 gm. of protein, for varying periods of time, and although the blood was not obtained at any particular time of day, yet it was generally taken midway between meals.

According to Widal,[19] the urea of the blood as determined by the hypobromite method varies from 30 mg. to 50 mg. per 100 c.c., with the latter figure as the upper limit of normal. Widal and Ronchese[20] state that normally the nitrogen of this urea makes up 77 to 79 per cent. of the total incoagulable nitrogen. This, however, is not in accord with the findings when more accurate methods are used, and it appears quite certain that normally the urea nitrogen makes up about 50 per cent. of the total incoagulable nitrogen as noted by Schöndorff,[10] Strauss,[5] Obermayer and Popper,[12] Folin and Denis[16] and Oszacki.[17]

Since Folin and Denis[16] have shown so strikingly that there is constantly a greater amount of incoagulable nitrogen in the blood of hospital patents, even though they have no manifest signs or symptoms of renal insufficiency, and since Farr and Austin[7] obtained such varying results in persons with apparently normal kidneys, it becomes very difficult to fix a normal figure for the incoagulable nitrogen of hospital patients. From our series, however, we are inclined to believe that an incoagulable nitrogen content of 40 or even 50 mg. per 100 c.c. of blood, does not necessarily imply a clinical renal insufficiency.

PERSONAL OBSERVATIONS

The patients studied have been a portion of those entering the medical service of the university hospital complaining of symptoms pointing either to a renal or cardiac insufficiency, or to both, together with a few classed as miscellaneous. All the cases were first arranged in a series according to diminishing phthalein output, and this is indicated by the number. It was evident, however, that there was a fairly definite group which could be separated from the others, having a low phthalein excre-

18. Widal, F., and Lemierre, A.: Ergebn. d. inn. Med. u. kinderh., 1909, iv, 548.
19. Widal, F.: Jour. Med français, 1911, v, 18.
20. Widal and Ronchese: Compt. Rend. Soc. de Biol., 1906, lx, 245.

tion and at the same time a low incoagulable nitrogen. This group constitutes those given in Table 2, and will be discussed later.

In Table 1 the observations are arranged in a series according to diminishing phthalein output. No relation between phthalein excretion and incoagulable nitrogen is evident until the phthalein output is definitely diminished. Patients 1 and 11 had nearly the same amount of incoagulable nitrogen, but in the former the phthalein excretion was 78 per cent. and in the latter 59 per cent. Cases 14 and 15, which clinically were very similar and in which the phthalein excretion was the same, differed markedly in the amount of incoagulable nitrogen.

Case 12, with a large amount of albumin in the urine, distinctly reduced chlorid excretion, normal phthalein elimination and normal incoagulable nitrogen, is of sufficient interest to report more in detail.

CASE 12.—The patient, aged 17, had a negative family history and had had the usual diseases of childhood with uneventful recovery. At 10 a curvature of the spine was noticed which has been progressive; at 15 the patient noticed the ankles swelling and puffiness under the eyes. Albumin, edema and weakness have been constantly present since. At the time of admission the patient looked pale, had slight edema of eyelids and ankles and complained of being tired on exertion. There were no visual disturbances and no cardiac enlargement, and the systolic blood-pressure was 130. The red blood-cell count was 4,900,000, the white 10,500 and there was 86 per cent. hemoglobin. The daily output of urine varied from 500 to 900 c.c. on an intake of 1,200 c.c. of fluid, with a specific gravity ranging around 1.012 and an albumin content of 4 to 6 gm. per thousand. There were a few casts in the sediment. Potassium iodid in 0.5 gm. dose gave no test in the urine after fifty-six hours. On an ordinary diet the patient excreted sodium chlorid, 2 to 4 gm., in twenty-four hours. An addition of 10 gm. of salt to her diet was followed by an elimination of only 2.05 gm. with no increase in the specific gravity or amount of the urine and was accompanied by a slight gain in weight. As noted above, the phthalein elimination and incoagulable nitrogen of the blood were within normal limits.

Widal[19] has made a distinct type of this form of nephritis (*chlorurémie*), having a large amount of albumin, no increase of the incoagulable nitrogen of the blood, and a distinct impermeability of the kidney to chlorids, and several cases showing a normal phthalein elimination have been reported by Pepper and Austin[21] and by Baetjer.[22]

In our series of patients, when the phthalein output fell to 40 per cent. or less, there was an accompanying increase in the incoagulable nitrogen with certain notable exceptions, namely, in the cases from which Table 2 is made up, and in Case 21. This latter was a case of double pyelonephritis, due to colon bacillus infection, with low phthalein excretion and low incoagulable nitrogen. We have studied but one such case and are unable to say why so chronic and active a process should give rise

21. Pepper and Austin: Am. Jour. Med. Sc., Feb., 1913, p. 254.

22. Baetjer, W. A.: Superpermeability in Nephritis, THE ARCHIVES INT. MED., 1913, xi, 593.

to no accumulation of nitrogenous bodies in the blood. The cases making up Table 2 will be discussed later.

Patient 27, who had chronic uremia, was under observation for some time, and shows very strikingly a falling phthalein excretion with an increasing amount of incoagulable nitrogen. Despite a further decrease in phthalein excretion, there was a sudden drop in the nitrogen content which remained practically constant. Three weeks elapsed between observations 27c and 27d, during which time the patient became edematous and hydremic. Edema and hydremia undoubtedly play an important rôle in the concentration of the incoagulable nitrogen, as has been noted by Hohlweg[13] and Strauss.[23] We would, therefore, explain this apparent discrepancy by assuming a condition of hydremia. The three cases in which there was no phthalein excreted showed a high incoagulable nitrogen, but it is seen that the two tests are not inversely proportional, since the highest incoagulable nitrogen was found in a case with about 10 per cent. phthalein excretion.

The relation of the urea-ammonia nitrogen to total incoagulable nitrogen varied greatly, from 23 per cent. in a patient with chronic parenchymatous nephritis to 96 per cent. in a patient with chronic uremia. In those patients who were uremic, however, the urea-ammonia nitrogen was in no case less than 71 per cent. of the total incoagulable nitrogen, but equally high percentages were obtained in several cases in which there was no nitrogen retention. Widal and Ronchese[20] have noted the increase of urea nitrogen over that of other nitrogenous substances in the blood of nephritics, but Foster[14] found that in uremia the urea nitrogen varied from 36 to 90 per cent. of the total incoagulable nitrogen, while similar observations have been made by Ascoli,[24] Obermayer and Popper,[12] Strauss,[15] and Folin and Denis.[16]

Since uremia has no definite symptom-complex, it should be stated at this point on what basis such a diagnosis has been made. We have taken the set of symptoms that Widal[18] has described as characteristic of *azotémie* or nitrogen retention, namely, great weakness and prostration, apathy, antipathy to food, muscular twitching, and a semistuporous condition. The clinical manifestations of uremia as we now know it are so varied that we regard it as very important to state definitely on what such a diagnosis is based. In none of our cases have there been marked gastro-intestinal symptoms or convulsions. Convulsions are probably not a part of pure nitrogen retention and ultimately we may be able to separate what we now rather loosely call uremia into several clinical entities. Strauss[15] has noted that there is no increase of the incoagulable nitrogen in uremia with convulsions.

23. Strauss, H.: Deutsch. Arch. f. klin. Med., 1912, cvi, 219.
24. Ascoli: Arch. f. d. ges. Physiol., Pfluger's, 1901, lxxxvii 103.

TABLE 1.—Result of Tests in Twenty-Four Cases

No.	Name	Diagnosis	Phthalein Excretion	Incoagulable Nitrogen	Urea Ammonia Nitrogen	Urea	Percentage of Nitrogen as Urea	Hypobromite Nitrogen as Urea	Remarks
1	U.	Chronic nephritis; chronic hypertension.	78	0.021	0.011	0.023	52.8	0.044	Blood-pressure 200. Urine: trace albumin and few casts.
2	R.	Chronic nephritis; acute thyroiditis and ethmoiditis.	77	0.012	0.008	0.017	67.5	0.031	Blood-pressure 185 to 235. Neuroretinitis. Albumin and casts heavy.
3	O.	Chronic nephritis; chronic hypertension.	75	0.024	0.018	0.039	74.0	0.068	Blood-pressure 140 to 170. Trace albumin and few casts. Neuroretinitis. Choked disk each eye.
4	C.	Hypertension (temporary).	72	0.038	0.019	0.041	50.0	0.036	Blood-pressure 140 to 200. No albumin or casts. Neuroretinitis.
5	Car. ...	Chronic hypertension; cerebral arteriosclerosis.	71	0.017	0.012	0.026	70.7	0.047	Blood-pressure 200 to 235. No albumin, few casts. Fundus arteriosclerotic.
6	Jos. ...	Toxic psychosis.	68	.....	0.009	0.019	. ..	0.032	Died. Necropsy showed thrombophlebitis, purulent bronchitis, emphysema, arteriosclerosis, chronic passive congestion, numerous hyaline glomeruli. No indican in blood.
8	Dunn. .	Chronic nephritis; arteriosclerosis; hypertension; myocardial insufficiency.	63	0.018	.....	.....	....	0.034	Blood-pressure 185 to 195. No albumin; few casts.
9	H.	Chronic nephritis; chronic hypertension.	40	0.033	0.011	0.023	33.5	0.048	Phthalein for one hour only. Blood-pressure 180 to 200. Distinct albumin and casts; no eye signs.
10	Ru. ...	Chronic hypertension; cystitis.	60	0.019	0.014	0.030	71.8	0.065	Blood-pressure 160 to 210. Trace albumin; few casts.
11	F.	Fibroid of uterus; secondary anemia.	59	0 025	0.006	0.012	24.0	0.044	Blood-pressure 175. Urine negative. Retinitis each eye.
12	Ter. ...	Chronic parenchymatous nephritis; chlorid retention.	58	0.014	0 003	0.007	23.1	0.024	Large amounts of albumin. Marked chlorid retention. Two weeks later phthalein excretion was 63.
13	Dra. ..	Syphilis; chronic nephritis; chronic hypertension; fibroid uterus; dilated aorta.	51	0.016	.....	.....	....	0.038	Blood-pressure 160 to 225. Large amounts albumin and casts. No marked fundus changes. Living in same condition eight months later.
14	L.	Chronic nephritis; chronic hypertension.	49	0.058	0.043	0.092	74.2	0.059	Blood-pressure 200. Faint trace albumin and few casts. Sudden death six months later.
15	Rus. ..	Chronic interstitial nephritis; chronic hypertension.	49	0.019	0.008	0.019	44.5	0.075	Blood-pressure 155 to 190. Trace albumin and few casts. Fundus arteriosclerotic.
17	We. ...	Pyelonephritis; myocardial insufficiency; mania.	39	.....	.....	.....	....	0.055	Blood-pressure 185. Albumin, casts and pus.

18	May ...	Chronic interstitial nephritis; uremia.	34	0.051	0.041	0.088	80.0	0.071	Blood-pressure 215 to 250. Much albumin and casts. Albuminuric retinitis. Some edema of eyes and limbs, cardiac hypertrophy, relative mitral.
19a	T	Chronic interstitial nephritis; chronic uremia.	33	.....	.....	.....	....	0.100	Blood-pressure 170 to 250. Much albumin and casts. Hemorrhagic retinitis. Observation below made one week later.
19b	.....	.....	29	.....	.....	.....	....	0.124	Died six weeks later in uremia.
21	Scan. ..	Pyelonephritis.	31	0.014	0.007	0.016	52.3	0.026	Blood-pressure 108. Trace albumin, few casts, much pus. Working daily and in fair condition five months later.
27a	J.....	Chronic interstitial nephritis; chronic uremia; cardiac dilatation and hypertrophy; hydrothorax.	17	.....	.....	.....	....	0.156	Blood-pressure 125 to 190. Heavy albumin and casts. Albuminuric retinitis. Died in uremia three months later.
27b	.....	.....	13	0.128	0.117	0.250	90.8	0.256	Eleven weeks ante mortem.
27c	.....	.....	..	0.141	0.128	0.276	91.1	0.288	Ten weeks ante mortem.
27d	.....	.....	10	0.060	0.048	0.104	80.0	0.138	Seven weeks ante mortem.
27e	.....	.....	7	0.059	0.044	0.096	75.5	0.134	Three weeks ante mortem.
28	Murr. ..	Myocardial insufficiency; chronic interstitial nephritis; hypertension; arterio sclerosis.	12	0.067	0.037	0.080	55.7	0 155	Blood-pressure 210 to 225. Heavy albumin and casts. Edema. Died five days later. No necropsy.
29a	Jock. ..	Chronic nephritis; uremia.	6	0.080	0.056	0.122	71.1	0.202	Blood-pressure 225 to 250. Urine: heavy albumin and casts. Albuminuric retinitis. Died in uremia six days later. No necropsy. Indican in blood positive.
29b	.....	.....	..	.....	.....	.....	....	0.328	Twenty-four hours ante mortem. Six hours ante mortem spinal fluid gave 0.358.
30	G.	Chronic nephritis; uremia.	0	0.100	0.084	0.181	84.5	0.437	Blood-pressure 120. Urine: albumin and casts. Indican in blood positive. Died in uremia thirty-six hours later. No necropsy.
31	Mid. ...	Chronic nephritis; chronic uremia; secondary anemia.	0	0.083	0.080	0.172	96.6	0.246	Blood-pressure 150 to 160. Urine: albumin and casts. Albuminuric retinitis.
32	Mc.	Uremia; anuria.	0	.....	.....	.....	...	0.474	Died six hours later. Necropsy showed hypernephroma of right kidney, chronic parenchymatous nephritis, chronic cystitis and pyelitis, chronic prostatitis with recent abscess, chronic vesiculitis, localized chronic meningitis. Endocardium sclerosed also coronary and renal vessels, obliterative endarteritis, chronic passive congestion, atrophy of all organs. Old syphilis (?).

As to the hypobromite method it is seen that its results varied greatly from those obtained by the Folin method. In general, the results by the latter are about 50 per cent. of those obtained by the hypobromite method, but when the nitrogen as urea made up a relatively larger part of the total incoagulable nitrogen the results by the Folin method approach those by the hypobromite method. In only three instances, in Cases 4, 14 and 18, were the results by the Folin higher than those by the hypobromite method. These variations may in part be due to an error in the hypobromite determinations, since only one analysis was made by this method, and also in the hypobromite determinations after precipitating with alcohol, as a second precipitation with zinc chlorid was not made. There is better agreement between the two methods when higher values are obtained and in spite of the wide variations we believe the hypobromite method to be a fair index of the urea content of the blood when there is a definite urea retention.

It is therefore evident that the hypobromite determinations must bear a rough relationship to the total incoagulable nitrogen. Table 1 shows that this relationship is not even so definite as that between the results obtained by the hypobromite method and the urea by the Folin method. This may be due to error in the hypobromite determinations or to its inherent faults, but with higher values the results are more in accord. Since the relationship between urea nitrogen and total incoagulable nitrogen is variable and since the hypobromite method is not an accurate method for urea determination, it is suitable as a guage of the incoagulable nitrogen of the blood only when there is a definite nitrogen retention, in which case the variables tend to disappear.

Table 2 is made up from those cases in which a diminished phthalein excretion was found with no increase of the incoagulable nitrogen of the blood. The symptoms of these patients without exception were those of cardiac insufficiency. In other words, these patients with cardiac insufficiency could eliminate nitrogenous products with ease but the kidneys showed a decreased permeability to phthalein. Hohlweg[13] found that cases of cardiac decompensation showed very little increase of the incoagulable nitrogen of the blood even when patients were moribund. Foster[14] found great variation in the incoagulable nitrogen of his uremic cases, but suggests that the cardiac element may be the explanation of the fatal issue in those cases having a low incoagulable nitrogen.

Rowntree, Fitz, and Geraghty[25] have shown experimentally that chronic passive congestion gives rise to a reduced phthalein excretion without marked increase of the incoagulable nitrogen. Rowntree and

25. Rowntree, Fitz and Geraghty: The Effects of Experimental Chronic Passive Congestion on Renal Function, THE ARCHIVES INT. MED., 1913, xi, 121.

TABLE 2.—Result of Tests in Nine Cases

No.	Name	Diagnosis	Phthalein Excretion	Incoagulable Nitrogen	Urea Ammonia Nitrogen	Urea	Percentage of Nitrogen as Urea	Hypobromite Nitrogen as Urea	Remarks
7a	Hep. ..	Cardiac insufficiency, dilatation and hypertrophy; chronic nephritis.	66	.....	.....	.....	...	0.046	Blood-pressure 200, falling to 120. Distinct albumin and casts. Much edema, chlorid retention. Retinal hemorrhages. Died seven months later of cardiac insufficiency. No necropsy.
7b	.....	.....	48	0.040	0.018	0.038	45.0	...	Five months ante mortem.
16	V.	Cardiac insufficiency; chronic nephritis; chronic gastritis.	42	0.015	.....	.....	....	0.038	Blood-pressure 155 to 170. Albumin and casts moderate. Retinal hemorrhages. Died two months later of cerebral hemorrhage.
20	S.	Myocardial insufficiency; mitral stenosis; auricular fibrillation.	32	0.016	0.009	0.020	56.5	0.046	Blood-pressure 120. Urine contains albumin and red blood-cells.
22	Up.	Myocardial insufficiency; chronic nephritis; arteriosclerosis.	31	.....	.....	.....	....	0.037	Blood-pressure 175 to 200. Albumin and casts positive.
23	Gar. ...	Myocardial insufficiency; mitral regurgitation.	28	. ...	. ...	.. .	....	0.081	Blood-pressure 150. Much albumin, few red blood-cells, few casts. Much edema and chlorid retention. Died one month later. Necropsy showed cardiac dilatation and hypertrophy; mitral valves sclerotic.
24	Do.	Myocardial insufficiency; arteriosclerosis; chronic nephritis (?).	26	0.021	0.010	0.023	51.4	0.031	Blood-pressure 170. Trace albumin and casts. Few fundus changes. Phthalein two weeks later was 36 per cent. In good condition five months later.
25	W.	Myocardial insufficiency; chronic nephritis; secondary anemia.	24	0.012	0.007	0.015	55.4	0.053	Blood-pressure 170 to 190. Trace albumin and casts. Albuminuric retinitis. Phthalein one week later was 55 per cent. Indican in blood negative.
26	Mor. ...	Cardiac insufficiency; chronic nephritis; lobar pneumonia.	22	0.031	0.022	0.047	69.9	0.080	Blood-pressure 180 to 200. Albumin and casts moderate. Fundus sclerotic. Died twelve days later. No necropsy.
33	Y.	Myocardial insufficiency.	..	.....	.....	.....	....	0.080	Blood-pressure 140 to 155. Urine heavy with albumin. Died thirty-six hours later. Necropsy showed cardiac thrombosis, syphilitic aortitis and myocarditis, chronic passive congestion, chronic parenchymatous nephritis with multiple infarcts, chronic prostatitis, cystitis, vesiculitis and pyelitis.

Fitz[26] found a low nitrogen content in their cases of pure cardiac insufficiency. Farr and Austin[27] had a similar experience and suggest that a low incoagulable nitrogen may serve as a means of separating cardiac cases. In our experience this has been true and by means of the incoagulable nitrogen of the blood we have been able to separate our cardiac cases from those with chiefly renal involvement.

From a diagnostic point of view the estimation of urea and the incoagulable nitrogen of the blood was found to be especially helpful in cases of coma and incipient "uremia"; in conjunction with the phthalein test it has enabled us to separate the cardiac cases.

As to prognosis all of the cases studied having an incoagulable nitrogen of 60 mg. or more per 100 c.c. of blood died within a period of weeks with symptoms of renal insufficiency, as did also all cases having a urea content of 100 mg. or more per 100 c.c. of blood by the hypobromite method. There was no relation between length of life and degree of nitrogen retention. Our experience as to the general significance of a high incoagulable nitrogen content is that of other observers and we believe it to be of great help in prognosis in those cases of nephritis in which there is a moderate reduction in phthalein elimination. A large percentage of our patients with cardiac insufficiency died and the estimation of the incoagulable nitrogen in these cases was not of the same value in prognosis as in diagnosis.

SUMMARY AND CONCLUSIONS

1. In general when the excretion of phenolsulphonephthalein was diminished below 40 per cent., there was a definite increase in the incoagulable nitrogen of the blood, except in one case of pyelonephritis and in those patients who were suffering chiefly from a cardiac decompensation.

2. The percentage of urea nitrogen to total incoagulable nitrogen varied widely but in cases of nitrogen retention it was uniformly high.

3. The hypobromite method gave high results which were inconstant but it served as a fair index of the urea content of the blood when there was definite nitrogen retention.

1000 East Ann Street.

---

26. Rowntree and Fitz: Studies of Renal Function in Renal, Cardiorenal and Cardiac Disease, THE ARCHIVES INT. MED., 1913, xi, 258.

27. Farr and Austin: Jour. Exper. Med., 1913, xviii, 228.

A COMPARISON OF METHODS OF OBTAINING ALVEOLAR AIR*

WALTER M. BOOTHBY, M.D., AND FRANCIS W. PEABODY, M.D.
BOSTON

The recent advances in our knowledge of the physiology of respiration and of the mechanism by which the normal reaction of the blood is maintained have opened wide fields for study in clinical medicine. In many of the problems which present themselves it is essential to have information regarding the tension of gases in the alveolae of the lungs. While it is comparatively simple to obtain satisfactory samples of alveolar air from trained workers, it is a much more difficult task when dealing with the average hospital patient, for unfortunately all the methods yet devised depend in part on the cooperation of the subject himself. Lack of intelligence, lack of interest, pain, dyspnea, restlessness, toxemia, unconsciousness and the natural disinclination of the sick person to take part in any active performance are among the many factors which interfere with the taking of reliable samples of alveolar air. Preliminary, therefore, to the study of alveolar air in pathological conditions, we have considered it necessary to make a comparative study of the various methods of obtaining alveolar air in order to determine the advantages and disadvantages of each method, the conditions under which a given method is best applicable, and in general to decide on which methods are most reliable for the study of clinical cases. The present report is based on approximately five hundred observations, on hospital patients, as well as on laboratory workers, most of whom were untrained in the methods of taking alveolar air.

THE HALDANE METHOD

The method as devised by Haldane[1] consists in the use of a ¾-inch hose about 4 feet long fitted with a glass mouthpiece at one end. The subject, after five minutes' normal breathing, gives the greatest possible expiration through the tube. This should be done rapidly to ensure the displacement of the air in the hose. At the end of the expiration the subject closes the mouthpiece with his tongue, and the sample of air is drawn from the beginning of the tube. Two samples should be taken—

* Submitted for publication Nov. 17, 1913.
* From the Surgical and Medical Services of the Peter Bent Brigham Hospital.

1. Haldane and Priestley: Jour. Physiol., 1905, xxxii, 225.

one from an expiration beginning at the end of normal inspiration, the other from an expiration beginning at the end of normal expiration. The values of the two samples are averaged.

This method is without doubt the best and simplest for the trained subject. For an untrained person, and especially for one of moderate intelligence, the use of the tongue in closing the mouthpiece presents an almost insurmountable difficulty. To overcome this we have modified the technic by introducing a specially constructed valve.

THE HALDANE METHOD WITH A SPECIALLY DESIGNED VALVE

The general objection to the use of a valve is that currents and eddies of air are formed which probably introduce a real element of uncertainty. While this is certainly true of the ordinary valve, we believe that the one to be described effectually overcomes this difficulty, and greatly increases the usefulness of the Haldane method.

The valve is a hollow copper cylinder about 4 inches in diameter and 1 inch long, closed at both ends. Set into each end of the cylinder, and opposite each other, are two brass tubes of ¾-inch diameter. Inside the main cylinder is another cylinder, ground so as to fit accurately, which revolves through an arc of about 45 degrees. The inside cylinder is pierced by two ¾-inch tubes, one of which is open at both ends, and so placed that when set opposite the two tubes previously mentioned a mouthpiece and straight tube about 4 inches long is formed. The far end of the tube is attached to a rubber hose 4 feet long, as in the ordinary Haldane alveolar air-tube. A single, almost instantaneous movement by means of a handle throws the second tube of the inner cylinder into communication with the mouthpiece. This tube is open at the side and closed at the far end, an arrangement which allows the subject to breathe naturally through the mouthpiece to the outside air with a dead space of not over 20 cm.

The apparatus is used as follows: The subject breathes naturally for five minutes through the mouthpiece directly to the outside air. At a given signal, at the end either of inspiration or of expiration, the observer turns the handle quickly and puts the subject into communication with a 4-foot tube that is perfectly straight and smooth. At the same instant the subject expires as deeply and rapidly as possible, and at the very end of the expiration the observer turns the handle back. The subject now breathes to the outside air and the alveolar air is sealed in the rubber tube. The sample is then quickly drawn into the sampling-pipet.

This method has proved itself to be of great value and we invariably use the valve when we are taking alveolar air by the Haldane method.

The relative accuracy of the Haldane method with and without the valve is shown by the following observation:

April 9, 9 a. m.; B.: With valve: Inspiration, $CO_2 = 41.1$ mm.; expiration, $CO_2 = 41.3$ mm. Without valve: Inspiration, $CO_2 = 39.9$ mm.; expiration, $CO_2 = 40.1$ mm.

The Haldane method in one of its various modifications should be classed as the standard method of taking samples of alveolar air since it undoubtedly gives the most accurate values when used under proper conditions. Its clinical applicability is limited to patients who are in comparatively good health. To obtain satisfactory samples it is necessary not only that the expiration should be as complete as possible, but also that it be rapid and forcible. A slow prolonged expiration is not sufficient. Many sick patients are unable, on account of pain or dyspnea or weakness, to give an expiration of enough force and depth. In these and in patients of distinctly low intelligence the method is unreliable. We have found, moreover, that even among intelligent, healthy persons it frequently takes considerable training before satisfactory results are obtained.

THE LINDHARD METHOD

Lindhard[2] has recently described the following very ingenious way of obtaining alveolar air: The subject breathes through a Krogh glass valve with rubber flaps and dead space of from about 40 to 50 c.c. Through an opening directly opposite the mouth is passed a small flexible lead tube with an interior bore of about 1 mm. This lead tube passes back into the pharynx so far as possible for comfort. The samples of air are drawn with a sampling-tube in 3 or 4 c.c. amounts at the end of a normal expiration. Accordingly to Krogh and Lindhard, this is reliable in subjects breathing 600 c.c. or over per respiration. The essential point in this method is the exact time at which the samples are taken, and this is somewhat difficult for the observer. If taken either just too early or too late alveolar air is not obtained. The movement of the rubber valve-flaps is an aid in timing.

We have made an extensive trial of this method and have found it to check up with the Haldane method if the subject breathed deeply. In the ordinary person 300 or 400 c.c. is the normal expired air; therefore, we were obliged to have the subject exhale about double his usual amount on a given signal; we repeated these deep exhalations about every forty-five seconds.

In order to determine more accurately the influence of the depth of expiration on this method of taking alveolar air, the valves were attached to a recording spirometer, and the volume measured of those expirations, at the end of which the samples were taken.

2. Linhard: Jour. Physiol., 1911, xlii, 337.

March 10, 3:30 p. m.; P.: Volume of expiration = 399 c.c.; alveolar CO_2 = 29.9 mm. Volume of expiration = 440 c.c.; alveolar CO_2 = 34.5 mm.
Control by two Haldane samples (valve) = 41.3 mm. and 38.9 mm.; 40.1 mm.

It is thus evident that samples taken at the end of normal expirations are not alveolar air. The percentage of carbon dioxid is much lower than it should be. The following experiments show the results which may be obtained when samples are taken at the end of deeper expirations:

April 3; P.: Volume of expiration = 880 c.c.; alveolar CO_2 = 40.2 mm.
Volume of expiration = 1,200 c.c.; alveolar CO_2 = 39.5 mm.
Volume of expiration = 1,650 c.c.; alveolar CO_2 = 36.5 mm.
Volume of expiration = 870 c.c.; alveolar CO_2 = 36.5 mm.
Volume of expiration = 1,000 c.c.; alveolar CO_2 = 38.8 mm.
Volume of expiration = 1,250 c.c.; alveolar CO_2 = 40.1 mm.
Control by two Haldane samples (valve); inspiration, CO_2 = 41.1 mm.
expiration, CO_2 = 41.6 mm.

April 4; P.: Volume of expiration = 650 c.c.; alveolar CO_2 = 38.0 mm.
Volume of expiration = 670 c.c.; alveolar CO_2 = 35.3 mm.
Volume of expiration = 840 c.c.; alveolar CO_2 = 37.8 mm.
Volume of expiration = 690 c.c.; alveolar CO_2 = 37.6 mm.
Volume of expiration = 840 c.c.; alveolar CO_2 = 39.6 mm.
Volume of expiration = 1,460 c.c.; alveolar CO_2 = 39.4 mm.
Volume of expiration = 880 c.c.; alveolar CO_2 = 39.2 mm.
Volume of expiration = 540 c.c.; alveolar CO_2 = 38.2 mm.
Volume of expiration = 800 c.c.; alveolar CO_2 = 38.3 mm.
Volume of expiration = 1,500 c.c.; alveolar CO_2 = 39.2 mm.
Control by two Haldane samples (valve); CO_2 = 38.5 mm.
CO_2 = 38.5 mm.

Inasmuch as these were the results obtained in a series of consecutive experiments with a subject who was not particularly well trained, it will be noted that they are in close accord with the results by the Haldane method. In the instances in which the carbon dioxid is low, beyond the limit of error, the timing of taking the samples was undoubtedly at fault. It is thus quite possible to obtain accurate samples of alveolar air by the Lindhard method even with persons whose respiration is normally shallow, if they are made to give occasional moderately deep expirations, and if a series of small samples are taken at exactly the end of such expirations.

Early in our studies we became impressed with the fact that untrained persons, and especially sick persons, were greatly inconvenienced by the use of valves. Indeed, the use of a simple mouthpiece may quite change the type of respiration, making it deeper than normal and more labored. This is especially the case with patients having a tendency to dyspnea. We therefore attempted to develop a method for obtaining alveolar air with as little as possible of the disturbing apparatus. The result is a modification of the Lindhard method.

THE LEAD TUBE METHOD

The subject breathes through his mouth, the nose as usual being closed by a nose-clip. A small flexible lead tube of 1 mm. bore is intro-

duced into the mouth, and the end passed as far back as is possible without bothering the patient. At a point about 3 cm. from the mouth a small feather is attached to the tube to serve as an index of the phases of respiration. The other end of the lead tube is attached to one of the sampling-pipets used by Krogh, with an easy working tap at the top, but none at the bottom. The opening at the bottom of the tube must be wide so that the mercury falls rapidly and the sample is taken quickly. The subject breathes naturally and at a word given at the end of an inspiration gives a deep forcible expiration of at least 600 or 800 c.c. At almost the end of the expiration the tap on the sampling-tube is turned quickly and from 3 to 5 c.c. of air taken into the tube from the back of the mouth. Deep expirations are given at intervals until a large enough sample is obtained for analysis. The following examples illustrate the probable accuracy of the method:

April 13; Miss B.: CO_2 in successive samples A. (1) 38.8 mm.; (2) 40.9 mm.; (3) 39.1 mm.; (4) 38.8 mm. B. (1) 40.8 mm.; (2) 42.0 mm.; (3) 43.1 mm.;
Controls by Haldane method: Inspiration, $CO_2 = 41.8$ mm.
Expiration, $CO_2 = 41.9$ mm.

These figures present some interesting points for study. It is probable that the tension of carbon dioxid in the alveolar air of this patient was practically 42 mm. Series A was taken by one of us and Series B by the other. We have frequently seen a slightly lower average by one observer than by the other. We attribute this to the difficulty of exactly timing the opening of the tap, and do not consider that it represents an actual change in the alveolar air. The following experiments were done by the same method:

April 14; F.: CO_2 in successive samples = (1) 40.4 mm. (2) 41.3 mm.; (3) 41.3 mm.; (4) 40.5 mm. Average = 40.8 mm.
Controls by Haldane method: Inspiration, $CO_2 = 39.1$ mm. Expiration, $CO_2 = 41.3$ mm. Average = 40.2 mm.
April 15; B.: CO_2 in successive samples = (1) 38.2 mm.; (2) 40.0 mm.; (3) 39.2 mm.; (4) 38.2 mm. Average = 38.9 mm.
Controls by Haldane method: Inspiration, $CO_2 = 37.2$ mm. Expiration, $CO_2 = 41.5$ mm. Average = 39.3 mm.
April 16; B.; CO_2 in successive samples = (1) 38.6 mm.; (2) 39.8 mm.; (3) 40.0 mm.; (4) 40.1 mm. Average = 39.6 mm.
Controls by Haldane method: Inspiration, $CO_2 = 38.9$ mm. Expiration, $CO_2 = 41.0$ mm. Average = 39.9 mm.
April 16; F.: CO_2 in successive samples = (1) 41.3 mm.; (2) 42.6 mm.; (3) 42.6 mm.; (4) 42.8 mm. Average = 42.1 mm.
Controls by Haldane method: Inspiration, $CO_2 = 40.0$ mm. Expiration, $CO_2 = 42.9$ mm. Average = 41.7 mm.
May 27; W. (patient): CO_2 in successive samples = (1) 42.4 mm.; (2) 43.0 mm. Average = 42.7 mm.
Controls by Haldane method: Inspiration, $CO_2 = 43.0$ mm. Expiration, $CO_2 = 41.4$ mm. Average = 42.2 mm.
June 2; S. (patient): CO_2 in successive samples = (1) 33.6 mm.; (2) 36.6 mm.; (3) 35.5 mm.; (4) 36.6 mm. Average = 35.6 mm.
Controls by Haldane method: Inspiration, $CO_2 = 35.3$ mm. Expiration, $CO_2 = 34.9$ mm. Average = 35.2 mm.

The chief disadvantage of the method is the difficulty of taking samples at exactly the right time. If they are taken too early or too late, the carbon dioxid values fall too low. It is thus advisable to take several tubes. Occasionally one analysis falls so far below the others that it is obviously incorrect and it must be discarded. The advantages of the method lie first in the fact that the valves or mouthpiece which upset the subject's natural respiration are discarded. Troublesome accumulation of saliva is avoided, as the tube can be removed from the mouth at any moment, and the subject allowed to swallow. Secondly, it is possible to obtain samples of alveolar air with less deep and forcible expirations than by the Haldane method because a number of small samples are taken from a series of expirations, rather than one large sample from a single expiration. In clinical work the method has proved to be of especial value with toxic or unconscious patients, in whom the alveolar ventilation is great. It is impossible to make these patients breathe as one desires, and their respiration is often changed when they are forced to breathe through a mouthpiece. Moreover, it is sometimes difficult to prevent leakage round a mouthpiece. The small lead tube can be passed into the mouth almost without the patients being aware of its presence, and the samples are taken at the end of expiration. The following analyses show the results obtained in a case of severe diabetic coma:

Oct. 2; B.: CO_2 in successive samples = (1) 6.2 mm.; (2) 6.2 mm.; (3) 5.5 mm.
Control by Plesch-Higgins method: CO_2 = 6.7 mm.
Oct. 3; B.: CO_2 in successive samples = (1) 11.0 mm.; (2) 10.8 mm.
Controls by Plesch-Higgins method: CO_2 = (1) 10.8 mm.; (2) 10.5 mm.

THE PLESCH METHOD

The principle of this method of determining the carbon dioxid tension of the alveolar air is quite different from that of the methods described above. Instead of attempting to obtain actual samples of air from the alveoli by means of deep expirations, Plesch[3] has suggested the rebreathing of a limited volume of air until it is in equilibrium with the air in the alveoli. Porges[4] and his associates have found this method satisfactory in series of clinical investigations. Porges states that the carbon dioxid diffuses so rapidly that an equilibrium is established before a single complete circulation of the blood has taken place. The apparatus, as we have used it, is the same in principle, and differs only in details of construction from that of Porges. The form was devised by Mr. H. L. Higgins, of the Carnegie Nutrition Laboratory, Boston. To a copper disk of about 20 cm. is soldered on the under side a flange 2 cm. wide. In the center of the same (under) side of the disk

3. Plesch: Ztschr. f. exper. Pathol. u. Therap., 1909, iii, 380.
4. Porges, Leimdorfer and Markovi: Ztschr. f. Klin. Med., lxxiii.

is soldered an ordinary ¾-inch three-way brass valve. Near this is soldered a small brass tap suitable for the attachment of small rubber tubing for taking samples of air. Over the top of the disk is stretched a woman's rubber bathing-cap, held in place on the flange by a large rubber band. The subject, with his nose clamped, breathes through a mouthpiece which is attached by a short piece of wide-bore rubber tubing to the three-way tap in the bottom of the copper disk. The tap is at first turned so that the subject breathes to the outer air. It is then turned so that the subject breathes in and out of the bag for a given length of time. The tap is then turned again, the bag is closed and a sample of air taken from the bag for analysis. Porges begins with the bag empty, lets the subject take a deep inspiration, and at the height of the inspiration turns the tap so that the subject expires into the bag and then rebreathes. Experiments with this technic, however, show that the tension of the carbon dioxid in the bag varies considerably with the depth of the initial inspiration, and thus with the amount of air in the system of respiratory tract plus bag. In the following the time and number of respirations were constant:

March 13; B.: Moderately deep initial inspiration: $CO_2 = 43.2$ mm.
Deeper initial inspiration: $CO_2 = 41.5$ mm.
Very deep initial inspiration: $CO_2 = 38.2$ mm.
Controls by Haldane method: Inspiration, $CO_2 = 41.2$ mm.
Expiration, $CO_2 = 41.2$ mm.

This source of error is to some degree at least avoided if one follows the suggestion of Higgins and fills the bag with a constant volume of air. The tap is then turned at the end of a normal expiration, and the patient begins by inspiring from the bag. This is the method which we have adopted, but instead of filling the bag with 600 c.c. of air (Higgins) we find it more satisfactory to fill with 1,000 c.c. of air, and thus allow the subject to take a deeper inspiration. The air is forced into the rubber bag through the small tap by water displacement from an ordinary flask.

The time during which breathing takes place is of considerable importance. Porges[4] states that after from twenty to thirty seconds there is very little change in the composition of the air. His experiments, however, show that practically there may be a considerable rise in the carbon dioxid tension if the same air is rebreathed for twenty-five-second periods after various intervals. We have performed a similar experiment and have found that after breathing from the bag four times in twenty seconds the carbon dioxid tension of the air in the bag was 39.5 mm. After an interval of three and one-half minutes the same air was rebreathed for two periods of twenty seconds each, the periods sepa-

rated by an interval of one minute. The carbon dioxid tension in the bag was then 45.9 mm. After rebreathing for two more similar periods the carbon dioxid tension had risen to 46.4 mm. There may also be a rise in the carbon dioxid tension if the length of the single periods is prolonged. Thus successive determinations with the same patient gave the following results:

Four respirations in 20 seconds: $CO_2 = 45.2$ mm.
Six respirations in 30 seconds: $CO_2 = 47.4$ mm.
Eight respirations in 40 seconds: $CO_2 = 48.6$ mm.

The element of time is therefore an important one, and we have found, in agreement to Porges, that from twenty to thirty seconds, and preferably twenty-five seconds, is the optimum.

The question of the rate and depth of respiration while rebreathing is of some moment. Within certain limits, however, they seem to play a lesser rôle than one might anticipate. The following successive determinations were made on the same person (P.) the rate and depth of the respirations being varied:

Five	respirations in 25 seconds.	Moderately deep	$CO_2 = 46.4$ mm.
Sixteen	respirations in 25 seconds.	Shallow	$CO_2 = 45.9$ mm.
Five	respirations in 25 seconds.	Very deep	$CO_2 = 46.3$ mm.
Seventeen	respirations in 25 seconds.	Shallow	$CO_2 = 45.4$ mm.
Five	respirations in 25 seconds.	Natural	$CO_2 = 39.0$ mm.
Five	respirations in 25 seconds.	Moderately deep	$CO_2 = 45.1$ mm.

Thus with the exception of the fifth determination, in which the subject was breathing naturally, quietly and superficially, the values of the carbon dioxid tension agreed well, whether the respirations were very deep or were shallow and rapid. Gentle, superficial respiration does not suffice to bring about complete diffusion of gases. The same has been found to be true of very rapid, superficial, panting breathing, which also gives too low values for the carbon dioxid tension. Respirations of moderate depth, however, seem to bring about as complete diffusion as very deep respirations. The results of a large number of determinations lead us to agree with Porges in feeling that the best results are obtained if five rather deep respirations are taken in the twenty-five seconds.

In regard to the accuracy and reliability of this method of taking alveolar air, one must first consider the constancy of the results obtained by the method and then the relation of the results obtained to those found by other methods. A comparatively large number of observations have now been made on patients and more or less experienced laboratory workers. The results depend, of course, in some degree on the experience of the subjects and on their intelligence in understanding what is required of them. In general, however, it has been striking that reliable observations have been obtained with comparative ease from almost all hospital patients. At least two experiments are made for each determina-

tion. The results very frequently agree within 1 mm. tension of carbon dioxid. Almost always they agree within about 2 mm. tension. While this is perhaps not the highest degree of accuracy, it must be remembered that it is extremely difficult to achieve greater accuracy in obtaining samples of alveolar air by any method except in trained subjects, so that on the whole the results are satisfactory as far as their constancy is concerned. A series of observations has also been made comparing those obtained by the Plesch method with those obtained by the Haldane method in the same subject and at the same time. The relation is, of course, a variable one, but the Plesch method almost always gives a higher value for carbon dioxid tension. On the average it is approximately from 1 to 4 mm. higher, but sometimes it is less and sometimes a little more.

The advantages in the use of the Plesch method are obvious. From the point of view of the subject it is extremely simple, and satisfactory results can be obtained from almost any one with a minimum of training. It is frequently extremely difficult to make a sick person or, in fact, many healthy persons, give an expiration of maximum depth, but almost any one can easily breathe deep enough to give reliable results by the Plesch method. Moreover, the technic required of the observer is so simplified that it is readily acquired and needs very little skill. The chief disadvantage of the Plesch method is that it is not quite so accurate as the Haldane method. This, however, seems to be only with regard to highly trained subjects. In a person of experience and intelligence it is possible to obtain constant and accurate results by the Haldane method, but in the average run of persons the results obtained by the Plesch method are on the whole more satisfactory. The Plesch method is worked out on a more empirical basis, but it gives very constant values, and values which are extremely satisfactory for comparative studies.

SUMMARY

As a result of an extensive comparative study of various methods for obtaining the tension of gases in the alveolar air, with especial reference to the use of these methods in clinical work, we have arrived at the following conclusion:

The Haldane method gives results which approximate closely the average gaseous composition of the alveolar air. It is the most reliable and accurate method when used on intelligent and experienced subjects. The necessity, however, of obtaining very deep and very forcible expirations limits its usefulness when working with untrained or sick persons.

The Lindhard method, and the modification of it described here, give values analogous to those of the Haldane method. The method has

the advantage, however, of not requiring such deep expirations as the Haldane method. The technic of taking the samples is, however, much more difficult for the observer. In certain types of pathological cases, notably in unconscious or very sick patients with a large alveolar ventilation, the method is useful and the technic simple.

The Plesch method gives values for the carbon dioxid tension which are higher than those obtained by the Haldane and Lindhard methods. Successive determinations give sufficiently constant values. The technic of the method both for the observer and for the subject is so simple that the method is especially useful for routine clinical work.

Peter Bent Brigham Hospital, 697 Huntington Avenue.

BOOK REVIEW

ORGANIC AND FUNCTIONAL DISEASES. A Text-Book of Neurology. By M. Allen Starr, M.D., Ph.D., LL.D., Sc.D., Professor of Neurology, College of Physicians and Surgeons, New York. Fourth edition, enlarged and thoroughly revised. Octavo, 970 pages, with 323 engravings and thirty plates in colors or monochrome. Cloth, $6.00, net. Lea & Febiger, Philadelphia and New York, 1913.

The fact that a text-book has reached a fourth edition is unmistakable evidence of its popularity, but when the subject is one undergoing rapid change there is always danger of unevenness of treatment and overlooking important details.

Dr. Starr's book has been justly noted for its clear manner of presentation, the fulness and accuracy of the clinical and anatomical descriptions and the judicious methods of treatment advised. In the present edition the good qualities are retained and in many details the work is brought well up to date. At the same time the reviewer can find some things that a more thorough revision might have changed for the better. The first chapter, for example, on the method of examination, is so sketchy as to be useless to a beginner—say an undergradute working in a clinic — and too conventional to be of value to the practitioner who wishes to refresh his knowledge of such matters. The anatomic account deserves similar criticism. Nevertheless, both methods of examination and anatomic details are considered in the course of the work, so that the criticism bears more on composition than on any lack of information. The latter is usually available and is always interesting as well as sound, as in the remarks on Freudian views and methods. As an evidence of the completeness of review we may cite the account of the changes in spinal fluid — so essential in diagnosis — and the chapter on poliomyelitis. Still, as a result of the rapid advance of knowledge, although the book includes references to work done in the early part of 1912, the discovery of the germ of poliomyelitis came too late to be included. As an evidence of unevenness the section on beriberi may be mentioned. In this practically no reference is made to the important researches on nutritional factors and the interesting subject of the vitamines. One wishes also that the author had discussed more fully the relation of pernicious anemia to spinal cord changes. The references to the Calmette test in the diagnosis of tuberculous infections and the finding of tubercle bacilli in the spinal fluid in meningitis are certainly based on insufficient consideration of the facts. On the other hand, all through the work one cannot but be impressed with the extent of the author's clinical experience and his familiarity with the literature, and their analysis up to the time of publication. The sections on treatment are usually full, judicious and well founded. It is all the more surprising then to find Warburg's tincture so highly praised for malarial affections, for that mixture has probably been most successful, outside of India, in the treatment of diseases in which the diagnosis of malaria has been anything but accurate. The aphoristic definition of parasyphilitic lesions as caused by syphilis, but not curable by antisyphilitic treatment is, perhaps, unduly pessimistic by reason of our rudimentary knowledge of methods of treatment. The important investigations of Noguchi and Swift suggest a better prospect. Perhaps it would be wrong to criticize the author for speaking of alcohol as a heart stimulant, but the direction for giving nitroglycerin hypo-

dermically in whisky or brandy shows a curious ignorance of the absorption of nitroglycerin. One must be grateful to the author for his candid condemnation of goat-lymph, so-called, so much abused by charlatans.

On the whole, the good points in the book so far outweigh the faults that the work is sure to prove in its present form a valuable aid and guide in the spread of neurologic information. It is unfortunate that it had to be printed on such heavy paper. Any gain that was intended for the illustrations was lost, for the latter vary much in quality and those for which the paper was perhaps chosen are not nearly as good as others.